Original Article

Therapeutic Drug Monitoring of Antiepileptic Drugs and Seizure Control

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Objective: The present study was aimed to determine effect of seizure control to Therapeutic drug monitoring [TDM] of antiepileptic drugs [AEDs].

Materials and Methods: The retrospective study was performed in outpatients who were attending the Epilepsy Clinic at Srinagarind Hospital, Khon Kaen University in 2011. The patients who were aged 15 or over, had enrolled in the Epilepsy Clinic for a minimum of 3 months and been treated with at least one AED were included into the study. The follow-up time was one year. Data on seizure control and TDM was collected from chart reviews and an electronic database. Data analysis was performed by using univariate analysis in SPSS 11.

Results: 382 patients received medical care at the clinic at a total of 2,369 times. Their average age was 40.35±0.83 years. Most (51.05%) were females. The average age epilepsy started to develop in the patients was 30.87±1.04 years, the average treatment period was 8.55±0.46 years with an average of 2.55±1.11 years of treatment in this clinic. The most common epileptic type was generalized tonic clonic seizure (59.42%), complex partial seizure (41.36%), and simple partial seizure (10.47%). The average number of seizures was 7.46±0.69 times/month. The percentage of seizure free was 55.54%. The drugs mostly used were Phenytoin (43.98%) and sodium valproate (40.44%). Therapeutic drug monitoring was carried out 185 times per 2369 clinical visits (7.81%). The indication of TDM requests were suspected sub-therapeutic level 79 times (41.80%), routine follow-up 75 times (39.68%), suspected toxicity 34 times (17.99%) and confirming drug level 1 time (0.53%). Plasma drug Concentrations appeared to be within therapeutic level 134 times (50.19%), sub-therapeutic level 69 times (25.84%), and over therapeutic level 64 times (23.97%). TDM requests was found to be significantly increasing in patients with uncontrolled seizure (p<0.05).

Conclusion: TDM is the necessary approach in helping multi-disciplinary team to manage use of medications appropriately.

Keywords: Therapeutic drug monitoring, TDM, Antiepileptic drug, Epilepsy

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Epilepsy is a frequently found neurological disease in people of all ages and sexes. The disease progresses chronically and needs continuous treatment. At present, epileptic patients account for over 50 million people and 85% of these are in developing countries. Only 10 to 40% receives appropriate treatment. There are 2.4 million new epileptic patients found each year[1,2]. The prevalence of epilepsy in Thailand is approximately 7.2 per 1,000 people[3]. There are significantly more reports of injuries from seizures than those from normal people, and the injuries found consisted of bruises, wounds, broken bones, scratches, sprains, or burns. The most frequently found injuries was brain injuries (74%)[4]. The hospitalization rates and mortality rates of patients with epilepsy are 2 to 3 times higher than normal people. Epilepsy affects mental health, causing stress, worries, distress and suicidal[5], sudden and unexpected death[6,7]. The rates of seizure control of the patients receiving single antiepileptic drug and the patients receiving new antiepileptic drugs [AEDs] are quite similar. 47% of patients are able to control seizures with the first type of AED while 14% are able to control

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seizures with the second or 3 AED types and 3% with two AEDs. Treatment failure can happen from drug withdrawal owing to unwanted symptoms from the drug used[8]. The average treatment period until the patient is able to control the symptoms is 2.6 years. Treatment methods can be changed in-between for 72.7%[9] of the case because physical response to drug of each patient differs in terms of pharmacodynamics and pharmacokinetics. Therapeutic drug monitoring is prediction of treatment efficiency and reduction of side effects that may occur from drug use. The present study therefore aimed to determine effect of seizure control to therapeutic drug monitoring [TDM] of antiepileptic drugs [AEDs].

Materials and Methods

The present study is a descriptive longitudinal study conducted with epileptic patients who received medical care at the Epilepsy Clinic, the Outpatient Department, Srinagarind Hospital from January 1, 2011 to December 31, 2011.

Inclusion criteria:

1) Diagnosed as having epilepsy

2) Aged 15 years or over

3) Treated with antiepileptic drug and received treatment at the Epilepsy Clinic, the Outpatient Department, Srinagarind Hospital for at least 3 months.

Exclusion criteria:

1) No medical record found at the Department of Medical Records

2) Transferred to another hospital

The data obtained was analyzed by univariate analysis in SPSS program Version 11. The variables with p-value <0.05 were further analyzed by means of the univariate analysis.

Results

There were 459 patients with epilepsy who received medical treatment and care at the Epilepsy Clinic, the Outpatient Department, Srinagarind Hospital from January 1, 2011 to December 31, 2011. From this number, we were able to compile complete required information of 382 cases. These patients received services at the Epilepsy Clinic for a total of 2,369 times. Their average age was 40.35±0.83 years. Most were females (51.05%). The average age the patients first developed epilepsy was 30.87±1.04 years. The average period of treatment at the Epilepsy Clinic was 2.55±1.11 years. The prevalent epilepsy types found was generalized tonic clonic seizure (59.42%), complex partial seizure (41.36%) and simple partial seizure (10.47%). The average number of seizures was 7.46±0.69 times per month. The patients with void of seizures accounted for 55.54%. The most common underlying disease was cerebrovascular disease (47.29%). The details of the patients' baseline data are shown in Table 1. It was found that 44% of the epileptic patients had at least one stimulating factor that caused seizures. The most frequently found stimulants were: lack of sleep (21.50%), stress (17.51%) and menstruation in females (7.14%). The antiepileptic drugs used mostly were Phenytoin (43.98%), Sodium valproate (40.44%), and Lamotrigine (13.89%).

The study reveals that the 7.81% of the patients received therapeutic drug monitoring. The reasons of physicians' order for TDM were

Table 1. Basic characteristic of patients

Characteristic	Results
Age (years) (n = 382)	
Mean ± SD	40.35±0.83
Gender (%) (n = 382)	
Female	195 (51.05)
Education (%) (n = 382)	
Uneducation	6 (1.57)
Elemantary school	84 (21.99)
Lower secondary school	30 (7.85)
High school/vocational certificate	72 (18.85)
Diploma/vocational diploma	23 (6.02)
Bachelor degree or higher	118 (30.89)
Types of epilepsy (%) (n = 382)	
Simple partial seizure	40 (10.47)
Complex partial seizure	158 (41.36)
Generalized tonic clonic seizure	227 (59.42)
Absence seizure	19 (4.97)
Atonic seizure	1 (0.26)
Myoclonic seizure	3 (0.79)
Tonic seizure	4 (1.05)
Status epilepticus	10 (2.62)
Lennox-gastaut syndrome	1 (0.26)
Epilepsy (unknown types)	39 (10.21)
Age at onset of epileptic seizures (years) (n = 340)	
Mean ± SD	30.87±1.04
Duration of treatment in epilepsy (years) (n = 340)	
Mean ± SD	8.55±0.46
Adherence 90% or higher (%) (2,196 visits)	2,089 (95.13)

n = number of patient's record

subtherapeutic level at 79 times (41.80%), routine follow-up at 75 times (39.68%), suspected toxicity level at 34 times (17.99%), and to confirm drug level-1 time (0.53%). The results of therapeutic drug monitoring were: on therapeutic level 134 visits (50.19%), subtherapeutic 69 times (25.84%), over therapeutic level 40 times (14.98%) and Toxic therapeutic level 24 times (8.99%) as shown in Table 2.

The univariate categorized by frequency of seizure, seizure <5 times/month is TDM request 6.8%, seizure 6 to 10 times/month is TDM request 15.6% and seizure >10 times/month is TDM request 16.1% shows that TDM requests was found to be significantly increasing in patients with uncontrolled seizure (p<0.05).

Discussion

This research found that the 7.81% of the patients under study were ordered to have TDM (185 visits out of 2,369 visit). The reasons for TDM orders were: subtherapeutic level (41.80%), routine follow-up (39.68%), suspected toxicity level (17.99%), and to confirm drug level (0.53%). The findings differ from the study of Nakariyakul K[10] and Affolter N et al[11] who found that routine follow-up accounted for the highest cases or 74.7 and 77%, respectively. The reasons for other examinations correlate to the present study. The results of therapeutic drug monitoring show that the drugs were within the therapeutic level for 50.19% of the cases, subtherapeutic for 25.84% of the cases, over therapeutic level for 14.98%, and toxic therapeutic level for 8.99% of the cases. This finding agrees with the study of Nakariyakul K[10] and Affolter N et al[11] who found that therapeutic level was the highest number of cases found. It was also shown that routine follow-up was the primary indicator for treatment. The present study, TDM requests was found to be significantly increasing in patients with uncontrolled seizure (p<0.05). Therapeutic drug monitoring [TDM] can prevent seizures, side effects from the use of antiepileptic drugs and enables the use of appropriate dose for each patient[12]. Therefore, the initial costs for treatment can be economized[13]. Hence, therapeutic drug monitoring should be performed, especially with the cases using the AED with short-range effectiveness. TDM orders for the patients receiving the new AEDs[12] are made when the patients have concurrent diseases such as renal failure or dialysis requirement, uncooperative patients in receiving drugs, and pregnancy. This is because TDM can increase the efficiency of treatment and reduce side effects.

Table 2. Plasma concentrations of AEDs

Characteristic	Results
Therapeutic drug monitoring (%) (n = 2,369)	185 (7.81)
Reasons for doctors requesting for TDM (%) (n = 189)	
Routine follow-up	75 (39.68)
Confirmation of suspected toxicity level	34 (17.99)
Confirmation of suspected subtherapeutic level	79 (41.80)
Confirmation of drug level	1 (0.53)
Plasma concentrations (%) (n = 267)	
Subtherapeutic	69 (25.84)
Within therapeutic	134 (50.19)
Over therapeutic	40 (14.98)
Toxic therapeutic	24 (8.99)

n = number of visit's record

Conclusion

TDM requests was found to be significantly increasing in patients with uncontrolled seizure (p<0.05). Therapeutic drug monitoring enables medical personnel to administer antiepileptic drugs appropriately for epileptic patients care and treatment.

What is already known on this topic?

TDM can prevent seizures, side effects from the use of antiepileptic drugs and enables the use of appropriate dose for each patient. This research found

Table 3. Effect of seizure control to TDM of AED

Seizure (times/month)	No TDM (%)	TDM (%)	Total (%)	p-value
<5	1,973 (93.2)	145 (6.8)	2,117 (100)	<0.05
6 to 10	92 (84.4)	17 (15.6)	109 (100)	
>10	120 (83.9)	23 (16.1)	143 (100)	
Total	2,184 (92.2)	185 (7.8)	2,369 (100)	

TDM requests was found to be significantly increasing in patients with uncontrolled seizure.

What this study adds?

This research found effect of seizure control to therapeutic drug monitoring [TDM] of antiepileptic drugs [AEDs]. This research study one year at the Epilepsy Clinic, the Outpatient Department, Srinagarind Hospital. Further Study could study long duration treatment in multicenter.

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Potential coflicts of interest

The authors declare no conflicts of interest.

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