Original Article

Adverse Drug Reactions of Anti-Epileptic Drugs in Epilepsy Clinic, Srinagarind Hospital

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Background: Epilepsy is an important neurological disease, making it necessary to receive appropriate treatment. Treatment with anti-epileptic drugs is the main treatment method for patients to be able to control seizures and to reduce the possible dangers that could occur to patients. Although anti-epileptic drugs are very useful for treatment, they may cause problems related to drug use, especially adverse drug reactions which are divided into 2 types: Type A reactions (Side-effects) and Type B reactions (Hypersensitivity reactions). Adverse drug reactions are important problems, which affect the abilities of the patients to control seizures and can lead to unsuccessful treatment results.

Objective: Therefore, the present study aims to examine the incidence rates of adverse drug reactions caused by taking anti-epileptic drugs, to appraise the patients' symptoms, and to inspect the drugs that are the causes and factors, which can affect the occurrence of adverse drug reactions among epileptic patients. The data have been useful to find methods to solve problems and to discover how to deal with patients when adverse drug reactions occur so that the findings can be apply to the future practices of patient care.

Materials and Methods: This research is a retrospective descriptive study. The data were collected from patients treated with anti-epileptic drugs at the Epilepsy Clinic at Srinagarind Hospital during the period between January 1, 2011 to December 31, 2011. The data were collected from the electronic data base of the Epilepsy Clinic and from the medical records of the outpatients at Srinagarind Hospital.

Results: There were 382 patients, who participated in the study. The most common medication which physician prescribed was Phenytoin (46.07%), followed by Sodium valproate (40.44%).The incidence of adverse drug reactions were discover in 230 cases (60.21%), including 183 cases of Type A reactions (Side effects) (47.91%) and 47 cases of Type B reactions (Hypersensitivity reactions) (12.30%). Adverse drug reactions from Type A reactions were found 221 times, and had primarily been caused by Phenytoin 109 times (49.32%) with the most common symptom being Gingival overgrowth, which was found 97 times (43.89%). Meanwhile, adverse drug reactions from Type B reactions were found 63 times and had mostly been caused by Phenytoin at 35 times (55.56%). The most common symptom was maculopapular rash, which was found 56 times (88.89%). When studying the correlation of the factors that can cause adverse drug reactions, it was revealed that when patients take more than one type of anti-epileptic drug, there is the risk of having Type A ADR and that risk is 4.25 times greater than for patients, who take only one type of anti-epileptic drug ($p = 0.039$). Regarding the rash caused by Phenytoin (Type B ADR), it was more commonly found in patients taking drugs which induce drug interactions at a rate of 5.39 times greater than those patients, who do not take the drugs which can induce drug interactions ($p = 0.02$).

Conclusion: According to the results of the present study, it was revealed that the adverse drug reactions caused by the anti-epileptic drugs taken by the epileptic patients represent important problems, whichwas commonly found. Phenytoin is the major cause of the incidences of both Type A reactions and Type B reactions. Therefore, those individuals, who are taking these medications, should be closely monitoring.

Keywords: Adverse drug reactions, Anti-epileptic drugs, Epilepsy

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Epilepsy is a common neurological disease and is consider as a major problem for the Thai Public Health system. The disease is chronic, making it necessary to receive continuous treatment. At present, it is estimated that there are approximately 50 million people with epilepsy around the world, with 2.4 million new cases of epilepsy being diagnose each year. Moreover, only 10 to 40 percent of these patients are receiving proper treatment[1,2].

In Thailand, the prevalence of epilepsy is approximately 7.2 per 1,000 people[3]. Currently, there have been 1,603 cases of patients admitted to Srinagarind Hospital and 646 cases of epilepsy treated in the Epilepsy Clinic[4].

The goal of treating epilepsy is to control seizures as completely as possible[5]. In the treatment of epilepsy,

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although anti-epileptic drugs (AEDs) are the main treatment, they can plausibly be the cause of drug related problems (DRPs)[6], including drug interactions and failure to receive medication, as well as adverse drug reactions (ADRs).

According to a study by Midlov P, et al[7], the most common problems associated with drug use in epileptic patients were adverse drug reactions and the improper selection of drugs. This is consistent with a study conducted by the epilepsy research group of Khon Kaen University[6], which discovered that adverse drug reactions were the most common problem (58.47%). The adverse drug reactions were classified into 2 types according to cause. Firstly, Type A (Side-effects) ADR refers to adverse drug reactions caused by the pharmacological effects of the drugs. Secondly, Type B (Hypersensitivity reactions) ADR refers to adverse drug reactions that could not predicted by pharmacological effects[8]. The adverse drug reactions may vary from each drug, depending upon different causation factors, such as the properties of some drugs, which have a narrow treatment range or which have the effect of inducing or inhibiting enzymes in other drugs; the type of the disease; and/or the basic characteristics of each individual patient[9]. The adverse drug reactions are important problem, which can affect the ability to control the patients' seizures[10]. Therefore, the purposes of this study were as follows: 1) to investigate the incidences of adverse drug reactions from the use of anti-epileptic drugs and 2) to determine which drugs were the causes and factors that affect adverse drug reactions in patients with epilepsy so that the methods to solve the problems can be discovered and proper care can be provided to the patients when the adverse drug reactions occur. The findings can lead to the establishment of better guidelines for patient care in the future.

Materials and Methods

Type of study

Retrospective descriptive study.

Sample

Epileptic patients, who had received anti-epileptic drugs at the Epilepsy Clinic of Srinagarind Hospital at the Faculty of Medicine of Khon Kaen University during the period between 1 January 2011 and 31 December 2011.

Methods

The data were collected from the electronic database of the Epilepsy Clinic and from the medical records of the outpatients at Srinagarind Hospital. It included basic information such as gender, age, medications, and information about the treatments given. Additionally, the information contained the period from the initial diagnosis of epilepsy, types of epileptic drug taken, any congenital diseases, other medications (supplements or herbs taken by the patients), all types of medicines that the patients had received, the types and symptoms arising from the adverse drug reactions, and the types of anti-epileptic drugs that had caused the adverse drug reactions, etc.

Data analysis

The obtained data were analyzed using descriptive statistics and was presented by frequency distribution, percentages or means, and standard deviations by SPSS version 20.0.

Results

According to the data obtained, there were 382 patients consisting of 187 males (48.95%) and 195 females (51.05%). The average age was 40.35$\pm$0.83 years (between 15 to 83 years of age). The patients had received Bachelor's degrees or higher at 30.89 percent and 55.76 percent were married. 202 of the patients had used universal health coverageat 52.87%. The average age for the onset of epilepsy was at 30.87$\pm$1.04 years old. The duration of epilepsy treatments had been 8.55$\pm$0.46 years on average and on average, 2.55$\pm$1.11 years when they had been treated at the Epilepsy Clinic. The three most common types of the epilepsy found were Generalized Tonic-Clonic Seizure (59.42%), Complex Partial Seizure (41.36%), and Simple Partial Seizure (10.47%). 43.72 percent of the patients were treated with one type of anti-epileptic drug, while 38.74 percent of the patients were treated with 2 types of anti-epileptic drugs. The most commonly prescribed anti-epileptic drugs were Phenytoin (46.07%) and Sodium Valproate (40.44%). On average, the seizures of patients occurred 7.46$\pm$0.69 times per month, and it was found that 55.54 percent of the patients had been seizure-free (Table 1).

Regarding the incidence of adverse drug reactions, it was found that there were 230 cases of adverse drug reactions out of all 382 patients (60.21%) with 183 cases (47.91%) of Type A reaction (Side-effects) and 47 cases of Type B reaction (Hypersensitivity reactions) (12.30%). There were 221 occurrences of Type A reactions ADR with the most common symptoms being 97 occurrences of gingival overgrowth (43.89%), followed 45 occurrences of tremors (20.36%), and 29 occurrences of weight gain (13.12%), respectively (Tables 2 and 3). Meanwhile, Type B reactions ADR were found 63 times, and the most common symptom was Maculopapular rash, which had occurred 56 times (88.89%) (Table 2).

Accordingly, there were the total of 183 cases of Type A reactions with adverse drug reactions occurring 221 times, which had mostly been caused by taking Phenytoin (109 occurrences or 49.32%), followed by Sodium valproate (85 occurrences or 38.46%) and Topiramate (9 occurrences or 4.07%) (Figure 1 and Table 3).

Meanwhile, the Type B reactions of 47 patients showed 63 occurrences of adverse drug reactions. The most common drugs found to cause Type B reactions were Phenytoin (35 occurrences or 55.56%), followed by Sodium valproate and Phenobarbital with (7 occurrences each or 11.11% each), and thirdly, Lamotrigine (5 occurrences or 7.94%) (Figure 2).

Since epilepsy is a chronic disease requiring patients to undergo treatment over a long period of time, various problems are likely to arise, which can be caused by taking

Table 1. Demographic data

Characteristic	Number of patients (%)
Gender	
Male	187 (48.95)
Female	195 (51.05)
Age (years)	
Mean ± SD	40.35±0.83
Min-max	15 to 83
Education	
Uneducation	6 (1.57)
Elementary 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)
Non-applicable	49 (12.83)
Status	
Single	152 (39.79)
Married	213 (55.76)
Widowed	10 (2.62)
Monk	7 (1.83)
Payer source	
Universal health coverage	202 (52.88)
Civil	118 (30.89)
Social security	39 (10.21)
Finance	23 (6.02)
Age at onset of epileptic seizures (years)	
Mean ± SD	30.87±1.04
Duration of treatment in epilepsy (years)	
Mean ± SD	8.55±0.46
Duration of treatment inclinical epilepsy	
Mean ± SD	2.55±1.11
Types of Epilepsy	
(patients have 1 or more types of epilepsy)	
Generalized tonic clonic seizure	227 (59.42)
Complex partial seizure	158 (41.36)
Simple partial seizure	40 (10.47)
Absence seizure	19 (4.97)
Tonic seizure	4 (1.05)
Myoclonic seizure	3 (0.79)
Atonic seizure	1 (0.26)
Non-specific types	50 (13.09)
Types of drugs	
(patients have 1 or more types of drugs)	
Phenytoin	176 (46.07)
Sodium valproate	154 (40.31)
Carbamazepine	45 (11.78)
Clonazepam	45 (11.78)
Phenobarbital	43 (11.26)
Lamotrigine	35 (9.16)
Levetiracetam	34 (8.90)
Topiramate	32 (8.38)
Diazepam	6 (1.57)
Oxcarbamazepine	4 (1.05)
Gabapentin	1 (0.26)
Others	1 (0.26)
Concurrent AEDs	
1 item	167 (43.72)
2 items	148 (38.74)
≥3 items	67 (17.54)

Table 2. Adverse drug reaction of anti-epileptic drugs

Adverse drug reaction	Number of event (%)
Type A reaction (side effect)	221 (100)
Gingival overgrowth	97 (43.89)
Tremor	45 (20.36)
Weight gain	29 (13.12)
Sedation	12 (5.43)
Weight loss	9 (4.07)
Ataxia	7 (3.17)
Alopecia	6 (2.71)
Nystagmus	4 (1.81)
Dizziness	4 (1.81)
Cognitive impairment	3 (1.36)
Diplopia	2 (0.90)
Mood disorder	2 (0.90)
Anemia	1 (0.45)
Type B reaction (hypersensitivity reaction)	63 (100)
MP rash	56 (88.89)
DRESS	2 (3.17)
Stevens Johnson syndrome	2 (3.17)
Exfoliative dermatitis	2 (3.17)
Angioedema	1 (1.59)

epileptic drugs. For example, adverse drug reactions may hinder desirable treatment results. Therefore, knowing the factors that can result in adverse drug reactions may help treatment teams to create plans that can assist in avoiding or preventing potential problems.

When the data were analyzed to find the relationship of the various factors affecting adverse drug reactions, it was divided into two parts. Part 1 consisted of the basic factors of the patients, and Part 2 consisted of the disease and treatment of the patients. It was found that when the patients were taking more than one type of anti-epileptic drug, they had a 4.25 times greater risk of experiencing Type A ADR than those patients, who were taking only one type of anti-epileptic drug (p = 0.039). Regarding the rashes resulting from Phenytoin use (Type B ADR), it was found in the patients, who were using drugs which induced drug interactions, had shown a 5.39 times greater incidence than those who had not used drugs that induced drug interactions (p = 0.02).

Discussion and Conclusion

According to the study of the occurrence of adverse drug reactions from anti-epileptic drugs, it was discovered that the patients, who had experienced adverse drug reactions, numbered 60.21 percent. In addition,79.57% of the adverse drug reactions were Type A reactions (Side-effects). The most common symptom was Gingival overgrowth, which was found at 43.89 percent or 25.39 percent of all patients in the study. This is consistent with a study conducted by Sunee Lertsinudom in 2009[6] and another study by Chaleewan Chaiklom in 2016[11]. Both of whom stated that gingival overgrowth had mostly been found at 60.28 percent and

Table 3. Anti-epileptic Drugs Categorized based on the Symptoms Causing Type A ADR

ADR (case)	PHT	VPA	CBZ	PB	TPM	LEV	LTG
Gingival overgrowth	97						
Tremor		45					
Weight gain		28				1	
Sedation	2	2	3	3		1	1
Weight loss		2			6		1
Ataxia	4	2	1				
Alopecia		6					
Nystagmus	4						
Dizziness			2		1	1	
Cognitive impairment	1				2		
Diplopia			2				
Mood disorder						2	
Anemia	1						
Total (%)	109 (49.32)	85 (38.46)	8 (3.62)	3 (1.36)	9 (4.07)	5 (2.26)	2 (0.90)

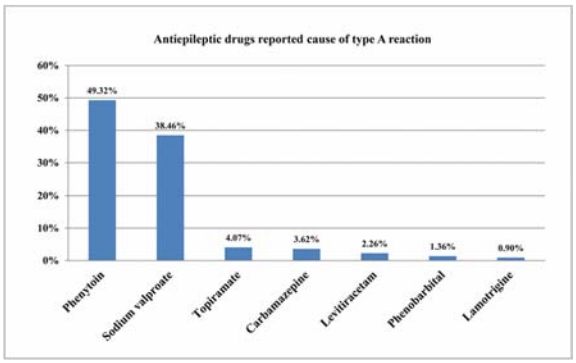

Figure. 1 The Anti-epileptic Drugs Reported as the Causes of Type A Reactions (Side-effects).

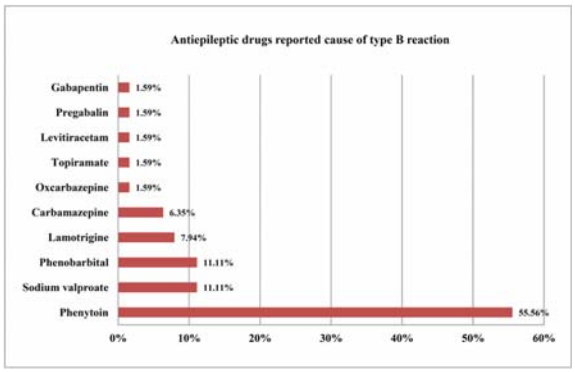

Figure. 2 The Anti-epileptic Drugs reported as the Causes of Type B Reactions (Hypersensitivity Reactions).

57.69 percent, respectively. Conversely, in 2008, Piyanida Senakam found that the most adverse drug reactions, which had arisen from epileptic drug usage, had been directly reported by the patients themselves. These had been dizziness (43.28%) and gingival overgrowth (25.37%)[12]. Meanwhile, Type B reactions were found to be at 12.30 percent. The most common symptom was Maculopapular rash (87.76%) caused by taking Phenytoin (55.56%). Similarly, Hirsch (2008)[13] found that the percentage of patients with skin rashes, who were receiving anti-epileptic drugs, had been at 14.3 percent. In contrast, Arif, H (2007)[14] reported an incidence of Type B reactions from taking anti-epileptic drugs at only 2.8 percent. However, the drug, that had most frequently caused Type B reactions, was Phenytoin (5.9%), which was found to be consistent with the present study. Regarding the correlation of the factors causing drug reactions from anti-epileptic drugs found in this study, it was revealed that the factors contributing to Type A reaction ADR was that patients had been using more than one type of anti-epileptic drug, while the factors causing Type B reaction was that the patient had used drugs that would induce drug interactions.

However, because the present study is a retrospective study and as such, it is incomplete in terms of a lack of data which focuses on the intensity of the ADR and the evaluation of the relationship of ADR occurrences using Naranjo's Algorithm. Furthermore, neither have solutions for preventing problems nor have guidelines for dealing with adverse drug reactions from using anti-epileptic drugs been thoroughly provided. At the very least, this study has shed light upon the incidences of adverse drug reactions from using anti-epileptic drugs, including the factors that may cause the likelihood of adverse drug reactions. Nonetheless, the data obtained from this study can be used as basic information for future research.

According to the findings from the current study, it was revealed that the adverse drug reactions, caused to patients with epilepsy by anti-epileptic drugs, are also important and commonly encountered problems. Moreover, these drug reactions may hinder the desired results of epilepsy treatments. Therefore, it is necessary to monitor the occurrences of adverse drug reactions, as well as to find ways to reduce the incidences of ADR. In addition, these findings

can, with the cooperation of medical personnel, be used to care for patients. When operating as a team, the medical personnel will be able to monitor patients together in order to prevent and handle such adverse drug reactions. This will allow patients to be safe when using epilepsy medications and will contribute to the effectiveness of treatment results.

What is already known on this topic?

The authors knew of the incidence rates of adverse drug reactions caused by taking anti-epileptic drugs and factors, which can affect the occurrence of adverse drug reactions among epileptic patients.

What this study adds?

The data have been useful to find methods to solve problems and to discover how to deal with patients when adverse drug reactions occur so that the findings can be apply to the future practices of patient care.

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Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. World Health Organization. Mental health [Internet]. 2012 [cited 2012 Nov 1]. Available from: https://www.who.int/mental_health/neurology/epilepsy/en/.
2. Prasat Neurological Institute. Clinical practice guidelines for epilepsy. Bangkok: Prasat Neurological Institute; 2011.
3. Asawavichienjinda T, Sitthi-Amorn C, Tanyanont W. Prevalence of epilepsy in rural Thailand: a population-based study. J Med Assoc Thai 2002;85:1066-73.
4. Hospital database of Srinagarind Hospital [Internet]. n.d. [cited 2012 Nov 22]. Available from:
5. North-Eastern Neuroscience Association. Management in patient who does not respond to new antiepileptic drugs. In: Clinical practice guidelines for epilepsy. Khon Kaen: Khon Kaen University; 2014. p. 49-53.
6. Lertsinudom S, Chaiyakom A, Tantapakun S. Management of drug related problems by pharmacists in epilepsy clinics Srinagarind Hospital. North East Thai J Neurosci 2009;4:39-50.
7. Midlov P, Bondesson A, Eriksson T, Petersson J, Minthon L, Hoglund P. Descriptive study and pharmacotherapeutic intervention in patients with epilepsy or Parkinson's disease at nursing homes in southern Sweden. Eur J Clin Pharmacol 2002;57:903-10.
8. Ningsanon T, Yothapitak C. Adverse drug reaction. Bangkok: Hospital Pharmacy Association (Thailand); 2007.
9. Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Adverse drug reactions. Bmj 1998;316:1295-8.
10. Tiamkao S, Lertsinudom S. Frequently asked questions about epilepsy for healthcare providers. Khon Kaen: KlungnanaVitthaya Press; 2010.
11. Jaiklom C, Ausavutmugkul T, Bunyapat N. Effect of pharmaceutical care in epileptic patients at prasat neurological institute. Bull Dept Med Serv 2016;41:110-9.
12. Senacom P, Jarernsiripornkul N, Uchaipichat V. Adverse drug reaction monitoring to antiepileptic drugs by patient self reports. Srinagarind Med J 2008;23:373-82.
13. Hirsch LJ, Arif H, Nahm EA, Buchsbaum R, Resor SR, Jr., Bazil CW. Cross-sensitivity of skin rashes with antiepileptic drug use. Neurology 2008;71:1527-34.
14. Arif H, Buchsbaum R, Weintraub D, Koyfman S, Salas-Humara C, Bazil CW, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. Neurology 2007;68:1701-9.