Pharmaceutical Care Improved Outcomes in Epileptic Patients

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ABSTRACT

The purposes of this study were to determine drug-related problems, clinical outcomes and humanistic outcomes after the provision of pharmaceutical care to epileptic patients taking phenytoin. Pharmaceutical care was provided to each patient throughout 6 months. The seizure frequency, DRPs and QOLIE-31 scores for each patient were recorded and compared during 6 months before and after the provision of pharmaceutical care. The study population consisted of 52 ambulatory epileptic patients. There were 24 men (46.15%). The mean age was 34 years (SD. 11.23). There were statistically significant differences ($p < 0.01$) between groups' seizure frequency, DRPs and overall QOLIE-31 scores in the periods before and after provision of pharmaceutical care. Before pharmaceutical care, the most frequent groups for seizure frequency were seizure-free (46.15%) and high frequencies (28.85%), while in the period after the provision of pharmaceutical care, the most frequent groups for seizure frequency were seizure-free (71.15%) and high frequencies (13.46%), respectively. That is the seizure frequency reduced after the provision of pharmaceutical care. We found a total of 111 DRPs in the period prior to provision of pharmaceutical care and 61 DRPs in the period after provision of pharmaceutical care. The most frequent DRPs were drug interaction, failure to receive the drug and adverse drug reaction. There were significant differences ($p<0.05$) in seizure worry, emotional well-being and medication effect domain functions. Pharmaceutical care practice has the potential to increase epileptic patients' quality-of-life scores and decrease both the frequency of seizures and number of drug-related problems.

Key Words: Epilepsy, Pharmaceutical care, Seizure, Drug related problems, QOLIE-31, Quality of life

INTRODUCTION

Approximately 1% of the general Thai population has epilepsy. It is therefore estimated that there are more than 600,000 epileptic patients in Thailand. The epileptic seizure affects patients' normal daily living and quality of life, both physically and psychosocially. Epileptic patients may not be able to work or drive normally and this can result in them being jobless and having other social problems. An epileptic seizure can cause severe physical injuries, burns, hypoxia and drowning due to respiratory arrest and aspiration. In addition, long standing epilepsy can result in brain damage and the longer the duration of epilepsy, the more difficulties there are in controlling the convulsions with medications. The mortality rate for those with epilepsy is 2-5 times higher than that for the general population due to accidents, suicide and sudden unexpected death (Chulalongkorn Comprehensive Epilepsy Program, 2001).

Phenytoin is an anticonvulsant drug frequently prescribed in adults and children. It is still one of the most popular antiepileptic drugs that is used in Thailand because of its cost and efficacy. Phenytoin is considered to be the drug of choice for partial and generalized tonic-clonic seizures. Presently, the approved uses of phenytoin include: primary or secondary generalized tonic-clonic seizures, simple and complex partial seizures, mixed seizure types including partial or generalized tonic-clonic seizures and tonic-clonic status epilepticus. Phenytoin has non-linear pharmacokinetics. The metabolic capacity for phenytoin is limited, therefore, modest changes in the maintenance dose can result in disproportionate changes in steady-state plasma concentrations. Furthermore, phenytoin has a narrow therapeutic index. The usual therapeutic range for total phenytoin plasma concentrations is 10 to 20 μg/mL (Winter, 1994). For these reasons, it is difficult to design the appropriate dosage regimens for phenytoin. When the plasma concentrations are lower than the therapeutic range, it may be ineffective. Conversely, when the concentrations are at the upper end of the therapeutic range, patients suffer side effects and toxicity, such as nystagmus, ataxia, incoordination, confusion, coma and even death if the plasma concentration is more than 100 μg/mL (Winter, 1994; Bauer, 2001; Lacy et al., 2001). In addition, many other factors affect the phenytoin plasma concentrations. For example, products from different manufacturers can cause variable bioavailability (Winter and Tozer, 1986; Suthisisang et al., 1998). Hypoalbuminemia is associated with high unbound fractions of phenytoin in the plasma. Hypoalbuminemia can be found among patients with liver disease or nephrotic syndrome, pregnant women, patients with cystic fibrosis, burn patients, trauma patients, malnourished persons and the elderly (Winter and Tozer, 1986; Winter, 1994; Bauer, 2001). Moreover, phenytoin may have drug interactions with high-protein-binding drugs such as valproic acid and warfarin. Such drugs can displace phenytoin from plasma-protein binding sites. Phenytoin is also prone to drug interactions with drugs that inhibit hepatic microsomal enzymes, eg., cimetidine, valproic acid, amiodarone, chloramphenicol, isoniazid, disulfiram and omeprazole. These drugs inhibit phenytoin metabolism and increase the plasma concentration of phenytoin (Winter, 1994; Bauer, 2001; Lacy et al., 2001).

Many of the characteristics of phenytoin mentioned above may result in drug-related-problems. Pharmaceutical care involves the process of identifying, resolving and preventing the drug-related problems by ensuring the most effective and safe use of drugs (Cipolle et al., 1998). For these reasons, pharmacists should provide pharmaceutical care to all patients but the number of pharmacists is not sufficient to do this, so we must select the high-risk patients for special care such as those patients taking phenytoin. The role of pharmacists in epilepsy clinics has been studied, although the researchers did not study outcomes such as humanistic outcomes (Allen et al., 1978; Summers et al., 1986; Kootsikas et al., 1990; McAuley et al., 1999). The purposes of this study were to determine the clinical outcomes (frequency of seizures), humanistic outcomes (quality of life) and drug-related problems after the provision of pharmaceutical care to epileptic patients taking phenytoin.

PATIENTS AND METHODS

The study had a prospective design and was approved by the Ethical Committee of the Faculty of Pharmacy, Chiang Mai University. Control patients who were not offered pharmaceutical care were not included in the study design for ethical reasons. If serious DRPs were observed in such a control group, a real possibility with this group of drugs, intervention to solve those problems would be contraindicated. This policy could have serious consequences for the patients concerned who would then have a legitimate cause for complaint.

Subjects

Seventy-five patients were selected for participation in the study and were recruited from the epilepsy clinic in Mahasarakham Hospital, Thailand. Twenty-three patients were lost to follow-up. The reasons for dropout included changes of the home locations, lack of time and changes of working locations. Thus the study consisted of 52 patients (follow-up participation rate 69%). The study population was ambulatory epileptic patients who were at least 15 years of age and were taking phenytoin. They might also take other antiepileptic drugs.

Patients were excluded from the study if they could not be followed-up throughout the study. Patients included were willing to sign a consent form, agreeing to participate in the study group. Patients were followed up every 1 or 2 months. The diagnosis was made by the physician in the epilepsy clinic. A nurse selected the patients who had epilepsy and were taking phenytoin for the study.

Interventions

The research pharmacist developed the pharmaceutical care manual for patients with epilepsy. The manual described the process of pharmaceutical care for epileptic patients and the patient's profile form.

The provision of pharmaceutical care process carried out by the research pharmacist had the following steps:

- Obtaining medication history
- Performing physical assessment of patients
- Evaluating laboratory data
- Reviewing current drug therapy for appropriateness
- Trying to identify patient-specific triggers and devise a plan to avoid them
- Assessing the patients' DRPs
- Measuring phenytoin serum concentration
- Consulting with the patient or physician and recommending relevant changes in drug therapy to physicians
- Providing patient education and consultation regarding disease, its management and drug therapy
- Giving a self-report book and the time and date of an appointment following each visit (the frequency of visits to the clinic was based on the severity of the patient's illness: follow- up every 1-2 months)
- The self-report book had a table for the patients to record the time that they took their antiepileptic drugs and the time that they had a seizure or experienced unusual symptoms.
- Monitoring patients for desired and undesired outcomes and compliance

The period of provision of pharmaceutical care for each patient was 6 months. The data collected by the research pharmacist were for a period of 6 months before and after the provision of pharmaceutical care.

Seizure Frequency Groups

The seizure frequency for each patient was collected for 6 months before and after the provision of 6-month pharmaceutical care. Seizure-frequency groups were based on the number of seizures in a year (Devinsky et al., 1995). Seizure-frequency groups were divided into four groups including a seizure-free group, a low-frequency group, a moderate-frequency group and a high-frequency group. In the seizure-free group, patients did not have a seizure. In the low-frequency group, there were 1-20 simple partial seizures or absence seizures or 1-4 complex partial seizures or 1 general tonic-clonic seizure. In the moderate frequency group, there were 21-100 simple partial seizures or absence seizures or 5-12 complex partial seizures or 2-4 general tonic-clonic seizures. In the high-frequency group, there were 101-200 simple partial seizures or absence seizures or 13-24 complex partial seizures or 5-12 general tonic-clonic seizures.

Classification of Drug-Related Problems

Drug-Related Problems (DRPs) were classified according to a modified version of Hepler and Strand (1990). Drug-related problems categorizations used were:

1. Untreated Indications,
2. Improper Drug Selection,
3. Sub-therapeutic Dosage,
4. Failure to Receive Drug,

5. Over-dosage,
6. Adverse Drug Reactions,
7. Drug Interactions,
8. Drug Use without Indication,
9. Others: other drug related problems that could not be grouped into any of the 8 categories above, such as relationships in the family or psychiatric problems that affected the care of the patients.

The DRPs were collected for a period of 6 months before and after the period of 6-month provision of pharmaceutical care.

QOLIE-31

The QOLIE-31 was developed to assess health-related quality of life in patients with epilepsy (Devinsky, 1993; Devinsky and Cramer, 1993; Meader, 1993; Perrine, 1993). It was derived from the QOLIE89 (Devinsky et al., 1995), an instrument with 89 items in 17 subscales including generic and epilepsy-specific issues. The QOLIE-31 questionnaire contains 31 items, 16 of which were drawn from existing sources and 15 were developed by the QOLIE Development Group. The QOLIE-31 contains seven multi-item scales that tap the following health concepts: seizure worry, overall quality of life, emotional well-being, energy fatigue, cognitive functioning, medication effects and social functioning. The scoring procedure for the QOLIE-31 converts the raw precoded numeric values of items having scores of 0-100, where higher scores reflect a better quality of life. An overall score is obtained by using a weighted average of the multi-item scale scores (Vickrey et al., 1993). The adaptation process of the QOLIE-31 into Thai included the following phases: translation into Thai, assessment of item comprehension, back translation into English, assessment of its validity by three experts and reliability (Kanjanasilp et al., 2004). The scores of QOLIE-31 prior to the provision of pharmaceutical care period were compared with those after the provision of pharmaceutical care period for each patient.

Statistical Analysis

A database was established and analyzed using SPSS 11.0 for Windows. Descriptive statistics are shown as means with standard deviations for continuous variables and frequencies with percent for categorical variables. Pearson's χ^2 tests were performed to examine associations between the frequency-seizure groups, categories of DRPs and periods of study. The scores of quality of life in the periods before and after the provision of pharmaceutical care were compared, using the paired t-test. Statistical significance was considered as $p<0.05$.

RESULTS

Seventy-five patients were selected for participation in the study. Twenty-three patients were lost to follow up. Thus the study consisted of 52 patients (follow-up participation rate 69%). There were 24 men and 28 women. The mean age of the participants was 34 years (SD. 11.23). Demographic and disease characteristics are

shown in Table 1.

Table 1: Demographic and disease characteristics (n=52).

Male	24 (46.15%)
Age (year)	34 ± 11.23
Weight (kg)	57.25 ±12.11
Height (cm)	160.08 ± 8.56
Phenytoin Dose (mg/d)	286.54 ± 48.62
Smoking (%)	9 (17.30)
Alcohol Drinking (%)	10 (19.23)
Type of Seizures	**Number (percent)**
Generalized tonic-clonic seizure	48 (92.31)
Complex partial seizure	1 (1.92)
Simple partial seizure	2 (3.85)
Tonic seizure	1 (1.92)

Frequency of Seizures

In the 6 months prior to provision of pharmaceutical care, the most frequent seizure frequency groups were seizure-free (46.15%) and high frequencies (28.85%), respectively. In the 6 months after the provision of pharmaceutical care, the most frequent seizure-frequency groups were seizure-free (71.15%), and high frequencies (13.46%), respectively. There were statistically significant differences ($p < 0.01$) between seizure-frequency groups in the periods before and after provision of pharmaceutical care. Numbers in the seizure-free group were 24 (46.15%) and 37 (71.15%), in the low-frequency group they were 6 (11.54%) and 3 (5.77%), in the moderate-frequency group they were 7 (13.46%) and 5 (9.62%), and in the high-frequency group they were15 (28.85%) and 7 (13.46%) in the 6 months before and after the provision of pharmaceutical care, respectively.

Drug-Related Problems

One patient could experience more than one DRP. We found a total of 111 DRPs in the 6 months prior to the provision of pharmaceutical care and 61 DRPs in the 6 months after provision of pharmaceutical care. The percentages of patients who had at least one DRP in the 6 months before and after the period of the provision pharmaceutical care were 90.38% and 75.00%, respectively. There were significant differences ($p<0.01$) between the number of DRPs in the periods before and after provision of pharmaceutical care. The number of DRPs in each category is shown in Table 2.

Table 2: Number of drug related problems in the 6 months before and after the provision of pharmaceutical care for 6 months.

DRPs	Pre (percent)	Post (percent)
1.Untreated Indications	0 (0.00)	0 (0.00)
2. Improper Drug Selection	1 (0.86)	1 (1.45)
3. Subtherapeutic Dosage	11 (9.40)	4 (5.80)
4. Failure to Receive Drug	24 (20.51)	7 (10.14)
5. Overdose	5 (4.27)	0 (0.00)
6. Adverse Drug Reaction	24 (20.51)	20 (28.99)
7. Drug Interaction	31 (26.50)	27 (39.13)
8. Drug Use without Indication	2 (1.71)	0 (0.00)
9. Others	19 (16.24)	10 (14.49)
Total	117 (100.00)	69 (100.00)
DRPs/patient	2.25	1.33

In the 6 months prior to the provision of pharmaceutical care, the most frequent DRPs were drug interactions (26.50%), failure to receive drugs (20.51%) and adverse drug reactions (20.51%) while in the 6 months after the provision of pharmaceutical care, the most frequent DRPs were drug interactions (39.13%) and adverse drug reactions (28.99%). Average DRPs per patient in the periods before and after provision of pharmaceutical care were 2.25 and 1.33, respectively. In the 6 months before provision of pharmaceutical care, 53.85% of problems were actual DRPs and 46.15% were potential DRPs. However, in the 6 months after the provision of pharmaceutical care, 46.38% of problems were actual DRPs and 53.62% were potential DRPs.

Quality of Life

The part of the study which investigated quality of life included 31 patients. Twenty-one patients could not or refused to answer the questionnaires (17 patients had psychosocial problems, abnormal brain function and handicap, 2 were elderly patients and 2 were unwilling patients). The characteristics of patients who completed the QOLIE-31 are shown in Table 3.

Table 3: Characteristics of patients who responded to QOLIE-31 (n=31).

Male	15 (48.39%)
Age (year)	32.84 ± 9.85
Weight (kg)	55.39 ± 11.52
Height (cm)	159.68 ± 8.91
Phenytoin Dose (mg/d)	283.87 ± 44.70
Smoking	29.03%
Alcohol Drinking	29.03%

Table 3: Characteristics of patients who responded to QOLIE-31 (n=31). (Continue).

Type of Seizures	Number (percent)
Generalized tonic-clonic seizure	29 (93.54)
Complex partial seizure	1 (3.23)
Partial seizure	1 (3.23)
Tonic seizure	0 (0.00)
Total	31 (100.00)

There were significant differences ($p<0.01$) of overall scores of QOLIE-31 between the 6 months before and after the 6-month period of the provision of pharmaceutical care. There were significant differences ($p<0.05$) in these 3 domain functions: seizure worry, emotional well-being and medication effects. There were no statistically significant differences ($p \geq 0.05$) in 4 domain functions: overall QOL, energy-fatigue, cognitive functioning and social function (Table 4).

Table 4: The scores of QOLIE-31 in the period before and after the provision of pharmaceutical care for 6 months (n=31).

Domain (total score)	Scores (pre-) (Mean ± SD)	Scores (post-) (Mean ± SD)	Sig.
Overall score (100.00)	61.15 ± 13.67	63.47 ± 16.11	0.002
Seizure worry (8.00)	4.12 ± 2.24	4.95 ± 2.32	0.014
Overall QOL (14.00)	9.59 ± 2.45	9.59 ± 2.61	0.489
Emotional well-being (15.00)	9.45 ± 2.74	10.03 ± 2.35	0.004
Energy-fatigue (12.00)	6.09 ± 1.70	5.98 ±1.69	0.092
Cognitive functioning (27.00)	14.71 ± 6.42	17.31 ± 4.80	0.054
Medication effects (3.00)	1.99 ± 0.88	2.04 ± 0.69	0.001
Social function (21.00)	15.21 ± 4.29	15.79 ± 3.70	0.093

DISCUSSION

Forty-eight (92.31%) patients in this study had generalized tonic-clonic seizures. Many reasons have been postulated for the poor control of seizures that people with low socioeconomic status obtain, including lack of access to healthcare providers, ineffectively-used medications, noncompliance and poor insight into the severity of their illness.

Pharmaceutical care, as defined by Hepler and Strand (1990) is "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve the patient's quality of life". Its goal is improvement of patient outcomes and quality of patient care and it involves identifying, preventing and resolving drug-related problems (DRPs). Several observational studies have examined the extent to which pharmacists identify and assist patients with DRPs. However, this is the first time that a study of outcomes of the provision of pharmaceutical care to

eplileptic patients has been undertaken.

Seizure-frequency group is a clinical outcome. Prior to providing the pharmaceutical care, the most frequent seizure-frequency groups were seizure-free (46.15%), and high frequency (28.85%). While in the period after provision of pharmaceutical care, the most frequent seizure frequency groups were seizure-free (71.15%), and high frequency (13.46%). These results indicate that a majority of patients could control their seizures after the pharmacist had provided pharmaceutical care. However, 7 patients still had many seizures and this might be due to their having a resistant form of epilepsy because they had experienced seizures for a long time. Consequently, they should adjust their treatment with other combinations of antiepileptic drugs and this would require more than the 6 months available in this study. Another reason might be due to the patients not being able to eliminate certain trigger factors such as drinking alcohol.

Drug-related problems are an important challenge to physicians and pharmacists and affect the patient's morbidity and mortality, as well as the patient's quality of life. DRP's may also have economic consequences for the patient and society. DRPs have been given many definitions, which may be summarized as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" (Van Mil, 1999). DRP's include untreated indications, improper drug selection, underdose, failure of patient to receive drug, overdose, compliance, drug interaction and drugs given without indications. These are not true outcomes but they were only clinical measures or processes (Holdford and Smith, 1997). The primary outcomes are the drug-related problems. Secondary outcomes are clinical outcomes (frequency groups) and humanistic outcomes (quality of life).

Average DRPs per patient before the provision of pharmaceutical care was 2.25 and that was similar to reported results in cardiology 1.9, geriatrics 2.0, respiratory medicine 2.1 and rheumatology 2.3 DRPs per patient (Viktil et al., 2004).

Frequencies of DRPs were reduced after the research pharmacists provided pharmaceutical care to epileptic patients for 6 months. However, some DRPs (75%) still continued including drug interactions, adverse drug reactions and failure to receive drugs.

The most frequent DRPs were drug interactions. Mostly, phenytoin interacted with other enzyme-inducer antiepileptic drugs (phenobarbital, carbamazpine) and valproic acid that can inhibit the enzyme metabolizing phenytoin. In addition, alcohol was also consumed by some patients in addition to phenytoin. However, these interactions should be monitored during therapy. Consequently, in the period after the provision of pharmaceutical care, these problems still existed. Other authors have suggested that "need for monitoring" should itself be considered an important DRP (Viktil et al., 2004).

All adverse drug reactions (ADRs) were actual DRPs. Mostly, ADRs are gingival hyperplasia. It may be due to many patients taking phenytoin for a long time. In such cases, pharmacists can only slow down the progress of this problem by

advising on oral hygiene. Thus, in the period after the provision of pharmaceutical care, this problem will need to be continually monitored.

Approximately 50% of the failures to receive the drug were actual DRPs. Several factors caused this problem including impairment of cognitive functions resulting from the patients being unable to remember and take their drug correctly, and also due to impairment of physical and psychological functions. Elderly patients may have difficulty understanding medication regimens and medical advice. Problems with visual acuity may hinder elderly patients' ability to take their medications appropriately. In addition, these patients did not have a caregiver. So in the period after the provision of pharmaceutical care, they still had some problems.

This study's findings are not consistent with those of other studies where dosage DRPs constituted about one-fourth of the DRPs recorded (Barber et al., 1997; Possidente et al., 1999). In this study, only 13.67% subtherapeutic dosages and overdosages were recorded. This may be because phenytoin and other antiepileptic drugs do not need to have the dose adjusted in patients with renal impairment as in other studies since phenytoin is metabolized by the liver.

The finding that the most frequent DRPs were drug interactions (26.50%), failure to receive drugs (20.51%) and adverse drug reactions (20.51%) is not consistent with other study results where the most DRPs in cardiology, respiratory and geriatric patients were nonoptimal dose, while the most DRPs of rheumatology patients were the need for additional drug (Viktil et al., 2004). It may be that cardiology and respiratory patients had impairments of renal functions while rheumatology patients had to use many new drugs. On the other hand, patients who were taking phenytoin tended to have more DRPs consisting of drug interactions and adverse drug reactions because phenytoin is a strong enzyme inducer and can cause many adverse drug reactions. Moreover, epileptic patients tend to have problems with cognitive functions and memory caused by antiepileptic drugs and their disease, and some have social problems, thus they may have more failures in receiving their drugs than patients with other diseases.

Health-related quality of life (HRQOL) is also considered a viable patients' outcome and an important measure of clinical or provider interventions (Pickard et al., 1999). An important component of HRQOL is health status which refers to whether an individual is free from the effects of disease and disability, able to perform the functions he or she desires and able to complete the usual activities of everyday living. QOLIE-31 is a disease-specific measure of quality of life for epileptic patients. There were significant differences ($p<0.01$) of overall scores of QOLIE-31 between the 6 months before and after the provision of pharmaceutical care. Although statistically significant, the results may not be clinically relevant, because only small differences between overall scores of before (61.15) and after (63.47) the provision of pharmaceutical care were found. However, results suggest that pharmacists have the potential to affect specific domains, such as seizure worry, emotional well-being and medication effects. These may be due to the response of patients to pharmacist counseling directly. In any case, overall QOL, energy-fatigue, cognitive functioning

and social function were not significantly affected by pharmaceutical care interventions. It should be noted that the responses to these domains may take more time in order to detect the differences and may be due to these domains being indirectly relevant to pharmacist counseling of epileptic patients.

The limitations of this study were that no control group who were not receiving pharmaceutical care was used (ethical reasons), the relatively small number of epileptic patients studied and the period of the provision of pharmaceutical care may be considered to be rather short.

CONCLUSION

The practice of pharmaceutical care has the potential to increase epileptic patients' scores of quality of life and decrease the frequency of seizures and drug-related problems. Although, pharmaceutical care affects patients' HRQOL, instruments more specific than the QOLIE-31 may be needed, or the services may need to be provided for more than 6 months in order to detect the differences in some domain functions. Treatment with phenytoin should evoke special awareness to monitor for DRPs during its use, and to have pharmacists included in the therapeutic health care team treating epileptic patients in the hospital and community. Epileptic patients should be provided with pharmaceutical care because all antiepileptic drugs cause many drug related problems. Epilepsy is a chronic disease and it also produces social and psychiatric problems for the sufferers.

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