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Research Article

MONITORING OF ANTICONVULSANT DRUG SIDE EFFECTS IN OUTPATIENTS WITH EPILEPSY

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ABSTRACT

Objective: This study aimed to monitor the side effects of carbamazepine, phenytoin, and valproic acid, and combinations of these drugs in adult patients with epilepsy, to raise awareness of the importance of drug side effect monitoring in hospitals.

Methods: In this prospective study, descriptive data were collected from patients who met the inclusion criteria of complete samples. Primary data were obtained using questionnaires, secondary data were collected from medical records, and analyses were performed using the Naranjo algorithm.

Results: Among the 54 included patients, 38 (70.37%) of them experienced drug side effects, and the most frequently observed side effect occurred in 48.15% of study subjects.

Conclusion: No correlation was identified between side effects and age (p=0.903) or gender (p=1.000).

Keywords: Carbamazepine, Naranjo algorithm, Phenytoin, Side effects, Valproic acid.

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INTRODUCTION

It is estimated that 2.4 million people are diagnosed with epilepsy annually, and 70% of those receiving proper therapy is free of side effects. In developing countries, however, 80–90% of epileptic patients do not receive proper treatment [1]. In Indonesia, 5–12 per 1000 people are diagnosed with epilepsy each year [2], and these patients are commonly treated with anticonvulsants. Special attention must be given when administering these drugs due to high rates of therapeutic failure, and because they often have narrow therapeutic indexes (TI) [3].

Anticonvulsants with narrow TI include carbamazepine, phenytoin, and valproic acid [4]. In all of these drugs, the difference between the toxic and the therapeutic dose range is small, which often leads to problems when dosages are changed slightly or in interactions with other drugs. According to a study by the University of Oslo and the Norwegian Pharmacy Association, 80% of 827 patients receiving drugs with narrow TI experienced drug-related problems, and only 67% did not experience any problems related to drugs [5].

Problems related to drugs include poor therapy efficacy, side effects, and high treatment costs [6-9]. Drug side effects are defined as harmful or unwanted responses at doses that are used for prevention, diagnosis, or therapy [10]. Side effects may also be related to individual susceptibilities and can, therefore, be managed by dosage adjustment or discontinuation of the treatment [11]. Accordingly, dose management is performed with careful monitoring of clinical side effects.

Side effects in patients consuming anticonvulsants with narrow TI may be influenced by gender and age. Moreover, based on a previous study, 25–30% of pregnant women experienced increased frequencies of seizures. Women also suffer from catamenial epilepsy, which increases the frequency of seizures during menstruation or ovulation [12]. These two conditions necessitate higher doses, which lead to increased serum concentrations of anticonvulsants, and increase the risk of side effects. Finally, the effects of age on rates of drug side effects have been related to changes in pharmacokinetics in elderly patients [13].

Indonesian Ministry of Health Regulation No. 72 2016 suggests that monitoring of drug side effects should be a pharmaceutical standard of care in hospitals. These investigators monitored the side effects of carbamazepine, phenytoin, and valproic acid, which are anticonvulsant drugs with narrow TI and have known side effects. Since monitoring of drug side effects is critical to the prevention of serious side effects of known or unknown causes, we collected qualitative and quantitative data from a series of patients and monitored drug side effects using the Naranjo algorithm [10].

This study was conducted at Fatmawati Central General Hospital, which is a Type A hospital with the highest referral for patients. Due to the extensive specialist and subspecialist services at this hospital, epilepsy is the fourth most frequent nerve disease treated in the outpatient department. The purpose of this study was to raise awareness of the importance of drug side effect monitoring in hospitals.

METHODS

Sampling

Data were collected from outpatients consuming carbamazepine, phenytoin, or valproic acid, or combinations of these drugs. Patients from the Fatmawati Central General Hospital were included according to the inclusion and exclusion criteria during the period from March to May 2017.

Validity and reliability tests of the questionnaire

Primary data were collected from the included patients using a questionnaire, which was subjected to validity and reliability testing. These tests were used to assess whether the questionnaire was sufficient for the study hypothesis and to assess its reliability according to within-subject consistency.

Data processing

Data from interviews and observations were checked for completeness, relevance of answers to questions, and consistency between questions. After editing all questionnaires, the data were coded by converting sentences and characters into numeric data and were then analyzed

using SPSS version 23. After analyzes of all data, code errors, omissions, and other inconsistencies were screened, and the data were cleaned by eliminating instances of missing variables and inconsistent data [14].

Data analysis

Data were analyzed using univariate and bivariate regression models, which returned frequencies and percentage rates for each variable [14]. Patient characteristics included age, gender, and data for anticonvulsant use, such as daily dosages and drug side effect classifications according to the Naranjo algorithm.

The Naranjo algorithm was used to qualitatively and quantitatively identify adverse drug reactions (ADR) following administration of the anticonvulsants carbamazepine, phenytoin, and valproic acid. The Naranjo algorithm is comprised of 10 questions, and the probability of side effects was determined based on total scores for all questions. These scores were classified into the categories of highly probable, probable, possible, and doubtful (Table 1) [10].

Characteristics or distributions of variables were used in bivariate analyzes of relationships between the side effects of carbamazepine, phenytoin, or valproic acid, and age and gender. Significant relationships were identified using Chi-square test [14].

RESULTS

Study subjects

During the period from March to May 2017, a total of 76 patients were administered carbamazepine, phenytoin, valproic acid, or a combination of those drugs in the Outpatient Department of Fatmawati Central General Hospital. 54 of these were included as study subjects, whereas 20 patients refused to participate, and 1 patient was excluded due to a diagnosis of cerebral palsy and tremors. Another patient was excluded because carbamazepine, phenytoin, or valproic acid therapy was stopped within 1 month. Patient characteristics are listed in Table 2.

Side effects

Observed side effects were divided into categories of probable and possible, with 26 (48.15%) and 12 patients (22.22%), respectively. Whereas 38 subjects (70.37%) experienced side effects, 16 (29.63%) did not (Table 3).

The results of this study showed that the present anticonvulsants were associated with different dominant side effects (Table 4).

DISCUSSION

Patient characteristics

Among the present 18–65-year-old patients, 51 (94.44%) were below the age of 60 and received carbamazepine, phenytoin, valproic acid, or a combination of these drugs. In a previous study, seizures and epilepsy were more frequently seen in patients over 60, and we included 3 (5.56%) elderly patients in this study. Seizures can be triggered by acute disease or can occur spontaneously. Epilepsy is also more common among the elderly, as indicated previously by greater numbers of first seizures in patients of 65 or above (136 subjects) than in those between the ages of 40 and 59 (50–60) [13]. Elderly subjects are comparatively few in our study and are not representative of the whole population, likely reflecting the short study period.

Numbers of female and male epileptic patients receiving carbamazepine, phenytoin, valproic acid, or a combination of these drugs were similar in our hospital, with 26 females and 28 male subjects. The percentage of female patients receiving anticonvulsants was 48.15%, and that of male patients were 51.85%. In a similar study published by Universitas Malta, the incidence of epilepsy in males was only slightly higher than

Table 1: Naranjo's probability scale

Total score	Category
9+	Highly probable
5–8	Probable
1–4	Possible
0	Doubtful

Table 2: Characteristics of epilepsy patients

Category	Number of patients n=54 (%)
Age	
Non-elderly (18–60 years)	51 (94.44)
Elderly (>60 years)	3 (5.56)
Gender	
Female	26 (48.15)
Male	28 (51.85)
Comorbidity	
Mental retardation	2 (3.7)
Tuberculous spondylitis	1 (1.85)
Hypertension	2 (3.7)
Post-stroke	1 (1.85)
Usage of single anticonvulsant	31 (57.41)
Carbamazepine	7 (14.81)
Phenytoin	12 (22.22)
Valproic acid	12 (22.22)
Combination	23 (42.59)
Carbamazepine and valproic acid	9 (14.81)
Phenytoin and valproic acid	14 (25.93)
Daily dosage	
Single carbamazepine	
2×200 mg	2 (3.70)
3×200 mg	5 (9.26)
Single phenytoin	
2×100 mg	2 (3.70)
3×100 mg	8 (14.81)
4×100 mg	2 (3.70)
Single valproic acid	
1×250 mg	1 (1.85)
2×250 mg	3 (5.56)
1×500 mg	3 (5.56)
2×500 mg	1 (1.85)
3×500 mg	1 (1.85)
1×750 mg	1 (1.85)
1×1000 mg	1 (1.85)
1×2000 mg	1 (1.85)
Combination of carbamazepine and valproic acid	
Carbamazepine	
2×200 mg	1 (1.85)
3×200 mg	4 (7.41)
4×200 mg	1 (1.85)
5×200 mg	1 (1.85)
1×300 mg	1 (1.85)
2×300 mg	1 (1.85)
Valproic acid	
1×250 mg	1 (1.85)
1×500 mg	3 (5.56)
1×750 mg	1 (1.85)
1×1000 mg	1 (1.85)
2×500 mg	1 (1.85)
2×1000 mg	1 (1.85)
3×250 mg	1 (1.85)
Combination of phenytoin and valproic acid	
Phenytoin	
3×100 mg	11 (20.37)
4×100 mg	3 (5.56)
Valproic acid	
1×250 mg	2 (3.70)
1×500 mg	2 (3.70)
1×750 mg	1 (1.85)
1×1500 mg	1 (1.85)
2×250 mg	3 (5.56)
2×500 mg	2 (3.70)
3×500 mg	2 (3.70)
4×500 mg	1 (1.85)

Table 3: Categories of side effects

Category	Total n=54 (%)
Naranjo's side effect category	
Highly probable	0 (0)
Probable	26 (48.15)
Possible	12 (22.22)
Doubtful	0 (0)
Did not experience any side effects	16 (29.63)

Table 4: Side effects experienced by patients

Category	Total n=38 (%)
Carbamazepine	
Diplopia	0 (0)
Disturbances in balance	2 (5.26)
Sleepiness	6 (15.79)
Dizziness	4 (10.53)
Nausea	1 (2.63)
Phenytoin	
Blurred vision	1 (2.63)
Dizziness	2 (5.26)
Fatigue	5 (13.16)
Valproic acid	
Gastrointestinal problems	1 (2.63)
Disturbances in balance	3 (7.89)
Tremor	6 (15.79)
Combination of carbamazepine and valproic acid	
Disturbances in balance	3 (7.89)
Sleepiness	4 (10.53)
Dizziness	3 (7.89)
Gastrointestinal problems	2 (5.26)
Tremor	3 (7.89)
Combination of phenytoin and valproic acid	
Blurred vision	4 (10.53)
Dizziness	7 (18.42)
Fatigue	3 (7.89)
Gastrointestinal problems	4 (10.53)
Disturbances in balance	1 (2.63)
Tremor	3 (7.89)

in females [15]. A study conducted by the Pharmacology Department of Universitas Aarhus also demonstrated no significant difference between numbers of male and female epileptic patients. Nonetheless, symptomatic epilepsy is more common in males, and cryptogenic epilepsy is more common in females [16].

Whereas epilepsy was the primary diagnosis in all of our subjects, some had other conditions, such as mental retardation (3.7%), tuberculous spondylitis (1.85%), hypertension (3.7%), and stroke (1.85%). This rate of mental retardation among epilepsy patients is low according to a study of 456,000 epileptic patients by the Joint Epilepsy Council of Great Britain and Ireland, who showed that 1 in 5 epilepsy patients had mental retardation [17]. Chronic hypertension has also been associated with the risk of epilepsy and is a well-described predictor of cerebrovascular diseases such as stroke. In elderly stroke patients, seizures are the most commonly seen neurologic symptom and usually occur within a few years after a stroke in around 10% of patients [18].

In this study, 57.41% of subjects received carbamazepine, phenytoin, or valproic acid only, and 42.59% received carbamazepine or phenytoin in combination with valproic acid. Whereas narrow TI is associated with single and combination anticonvulsant therapy, neurology related side effects such as dizziness, sleepiness, and fatigue are reportedly more common with combined anticonvulsant therapy. These investigators also reported that only a few patients did not experience seizures during combined anticonvulsant therapy [19].

The present dosage regimens (Table 2) were most commonly single or combination therapies of carbamazepine, phenytoin, and valproic acid at 3×200 (16.67%), 3×100 (35.18%), and 1×500 mg/day (14.82%), respectively.

Side effects

The most frequently observed side effect of carbamazepine was sleepiness and was documented in 6 subjects (15.79%). Carbamazepine can decrease the duration of rapid eye movement (REM) and non-REM 3 sleep stages, thereby reducing sleep quality [20].

In contrast, phenytoin caused fatigue in 5 of our subjects (13.16%) and 531 out of 12,077 people in a study by the Food and Drug Administration [21].

In the present and previous studies, valproic acid most commonly causes side effects of tremor, which was seen in 6 patients (15.79%), and is a reported effect of long-term use of valproic acid. Since valproic acid increases glutamate metabolism, it increases circulating ammonia concentrations. Under normal conditions, serum ammonia is present at 10–40 μmol/L and causes tremors at 120 μmol/L [22]. According to a study by the WHO, tremor is the most common side effect of valproic acid [1]. Sleepiness is the most common side effect of combination therapy with carbamazepine and valproic acid and was observed in 4 of our patients (10.53%). Accordingly, serum carbamazepine concentrations were previously associated with sleepiness [12]. In patients receiving the combination of phenytoin and valproic acid, the most commonly observed side effect was dizziness (7 patients; 18.42%). Accordingly, dizziness was previously associated with serum phenytoin concentrations of 20 mg/mL [23].

Relationships of drug side effects with gender and age

Among the 26 female subjects, 19 (73.1%) suffered side effects of anticonvulsants. Similarly side effects occurred in 19 out of the 28 (67.9%) male subjects, and no significant sex-related differences were identified in Chi-square test (p=0.903). The Chi-square test resulted in a score of <5; therefore, the p score in the continuity correlation was used [24]. However, female subjects with epilepsy experience various physiological changes that may affect the types of side effects experienced. In particular, increased ratios of estrogen to progesterone during menstruation are a likely contributor to clinical outcomes, as estrogen and progesterone have mild epileptogenic and antiepileptogenic properties, respectively. This was previously indicated by increased frequencies of seizures during menstruation in female patients with partial epilepsy, and the resultant necessity of higher dosages leading to increased susceptibility to side effects [2]. Comparatively, low estrogen hormone levels in males should be accompanied by lower [25] and less variable seizure rates, precluding changes in doses and fewer side effects.

In the present study, side effects were observed in 70.6% of non-elderly subjects and 2 out of 3 elderly subjects (66.7%), but no significant age-related differences were identified in Chi-square test (p=1.000). The management of elderly epileptic patients, nonetheless, requires caution due to reduced organ function and basal metabolic rates [2]. Anticonvulsant pharmacokinetics have also been shown to change in the elderly [13], reflecting reduced liver mass and hepatic metabolism, which is required for clearance of some anticonvulsants. Reduced kidney function also limits creatinine clearance of anticonvulsants, and carbamazepine creatinine clearance was reportedly 30–40% less in elderly patients [13]. Finally, albumin concentrations are reduced in the elderly, and because carbamazepine, phenytoin, and valproic acid have high protein-bound percentages of 40–90%, 90%, and 90–95%, respectively, albumin concentrations of <3.5–4.5 g/dL may limit clearance of these drugs in the elderly. These three pharmacokinetic changes all contribute to increases in serum concentrations of drugs in the elderly, which leads to higher susceptibility to side effects [13].

CONCLUSION

Based on the results of this study, we conclude that patients receiving anticonvulsant drugs are mostly non-elderly (94.4%) and are most commonly treated with single anticonvulsant drugs (57.41%). Whereas

side effects were categorized as probable with a percentage of 48.15% and possible with a percentage of 22.22%, the most commonly observed side effect was dizziness (18.42%) due to combination treatment with phenytoin and valproic acid. Finally, no significant relationships between side effects and age and gender were identified.

CONFLICTS OF INTEREST

All authors have none to declare.

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