ORIGINAL ARTICLE

Prevalence of Comorbid Diseases and Drug Interactions in Persons with Epilepsy Treated at a University Hospital

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Objective: To report prevalence of comorbid diseases and potential drug interaction in persons with epilepsy who had comorbid diseases in a University Hospital.

Materials and Methods: This was a retrospective descriptive study conducted at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. The authors performed a search on hospital database by using the code of the International Classification of Diseases 10th Revision (ICD-10) for epilepsy (G40). The inclusion criteria were adult patients with an age of 18 years or over who treated and recorded by the hospital database. The study period was between January 1st, 2015 and December 31st, 2020. Prevalence of comorbid diseases and drug interactions of patients with epilepsy were reported.

Results: There were 1,288 persons with epilepsy met the present study criteria. Of those, 565 patients (46.01%) were male. The average (SD) age of all patients was 47.00 (SD 18.86) years. There were 450 patients (36.64%) who had at least one comorbid disease. The top four comorbid diseases were hypertension (73 patients; 16.22%), cerebrovascular diseases (56 patients; 12.44%), diabetes (55 patients; 12.22%), and dyslipidemia (48 patients; 10.67%). The top 10 drug interactions between anti-epileptic drugs and the treatment of comorbid diseases were detected. Of those, one pair had major severity, while the other nine pairs were moderate severity. The top three drug interactions were folic acid/phenytoin (24.90%), aspirin/sodium valproate (19.18%), and simvastatin/ phenytoin (13.06%).

Conclusion: Hypertension was the most common comorbid disease in persons with epilepsy. Drug interactions between anti-epileptic drugs and prescribed medications for comorbid diseases should be aware.

Keywords: Hypertension; Diabetes; Cerebrovascular diseases; Folic acid

Received 6 March 2024 | Revised 2 May 2024| Accepted 9 May 2024

J Med Assoc Thai 2024;107(Suppl. 1):S86-90

Website: http://www.jmatonline.com

Epilepsy is a common neurological disease. Its incidence rate was 61.4 per 100,000 person-years (95% confidence interval of 50.7 to 74.4) but was as high as 139.0 per 100,000 person-years in the low/middle-income countries[1]. Persons with epilepsy are at risk for having comorbid diseases eight times than general population including depression, heart disease, or sleep apnea[2-4]. These comorbid diseases may cause further several diseases or poor quality of life[5-10]. A population study found that persons with epilepsy had higher risk for somatic/ psychiatric comorbidities and cognitive dysfunction for 5.44 times and 28.1 times, respectively[10].

A national database study in Thailand found that the two most common comorbid diseases in persons with epilepsy were hypertension (10%) and diabetes mellitus (4.6%). These two diseases or other diseases may result in more medications to treat those comorbid diseases. These additional medications may have drug interaction with the anti-epileptic drugs. As comorbid diseases may be found up to 98.3% in the elderly persons with epilepsy[11], physicians should be aware of drug interactions in individuals with epilepsy. Currently, there is limited data in literatures on prevalence of potential drug interactions in persons with epilepsy who have comorbid diseases particularly in Thailand. This study aimed to report potential drug interaction in persons with epilepsy who had comorbid

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How to cite this article:

Chatchamni M, Chainirun N, Mungmanitmongkol S, Sawanyawisuth K, Tiamkao S. Prevalence of Comorbid Diseases and Drug Interactions in Persons with Epilepsy Treated at a University Hospital. J Med Assoc Thai 2024;107(Suppl.1):S86-90

DOI: 10.35755/jmedassocthai.2024.S01.S86-S90

diseases in a real-world practice.

Materials and Methods

This was a retrospective descriptive study conducted at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. We performed a search on hospital database by using the code of the International Classification of Diseases 10th Revision (ICD-10) for epilepsy (G40). The inclusion criteria were adult patients with an age of 18 years or over who treated and recorded by the hospital database. The study period was between January 1st, 2015 and December 31st, 2020. The study protocol was approved by the ethics committee in human research, Khon Kaen University, Thailand (HE631294).

Eligible patients were retrieved for clinical data including age, sex, comorbid diseases, anti-epileptic drug treatment, and the treatment of comorbid diseases. Drug interactions between anti-epileptic drugs and medications for the treatment of comorbid diseases were checked by Lexicomp® Mobile Application Software. Drug interactions were reported for severity (mild, moderate, and major), details of drug interactions, and percentage of patients who were at risk.

Statistical analysis

Descriptive statistics were used to calculate mean (SD) for numerical variables and number (percentage) for categorical variables. Analyses were performed by using Microsoft Excel 2010.

Results

There were 1,288 persons with epilepsy met the study criteria. Of those, 565 patients (46.01%) were male. The average (SD) age of all patients was 47.00 (SD 18.86) years; categorized as adult patients for 876 patients (71.34%) and elderly patients for 352 patients (28.66%). There were 450 patients (36.64%) who had at least one comorbid disease. Of those, 255 patients (20.77%) had one comorbid disease, 112 patients (9.12%) had two comorbid diseases, 56 patients (4.56%) had three comorbid diseases, 17 patients (1.38%) had four comorbid diseases, and 10 patients (0.81%) had five or more comorbid diseases. The top four comorbid diseases were hypertension (73 patients; 16.22%), cerebrovascular diseases (56 patients; 12.44%), diabetes (55 patients; 12.22%), and dyslipidemia (48 patients; 10.67%) as shown in Table 1.

Regarding anti-epileptic drugs (Table 2), most patients received either two or three drugs (359 patients; 79.78%). The top four anti-epileptic drugs were sodium valproate (56.00%), phenytoin (47.56%), levetiracetam (41.33%), and clonazepam (30.89%). Regarding comorbid diseases (Table 3), 83 patients (18.44%) had one medication for the treatment of comorbid disease and eight patients (1.78%) received 10 or more medications for the treatment of comorbid diseases. The top four medications for the treatment of comorbid disease were folic acid (28.00%), aspirin (18.67%), Simvastatin (14.00%), and vitamin B complex (13.56%).

There were 10 drug interactions between anti-epileptic drugs and the treatment of comorbid diseases were shown

Table 1. Details of comorbid diseases of persons with epilepsy (n=1,228).

Comorbid diseases	Number (%)
Hypertension	73 (16.22)
Cerebrovascular diseases	56 (12.44)
Diabetes mellitus	55 (12.22)
Disorders of lipoprotein metabolism and other lipidemias	48 (10.67)
Arthropathies	17 (3.78)
Anxiety	16 (3.56)
Soft tissue disorders	16 (3.56)
Atrial fibrillation and flutter	15 (3.33)
Chronic kidney disease	14 (3.11)
Malignant neoplasms	12 (2.67)
Mental disorders due to known physiological conditions	11 (2.44)
Cerebral palsy and other paralytic syndromes	11 (2.44)
Disorders of the thyroid gland	9 (2.00)
Mental and behavioral disorders due to psychoactive substance use	9 (2.00)
Inflammatory diseases of the central nervous system	9 (2.00)
Migraine	9 (2.00)
Diseases of liver	9 (2.00)
Allergic rhinitis	8 (1.78)
Other congenital malformations	8 (1.78)
Ischemic heart diseases	7 (1.56)
Intellectual Disabilities	6 (1.33)
Extrapyramidal and movement disorders	6 (1.33)
Sleep apnea	6 (1.33)
Chronic rheumatic heart diseases	6 (1.33)
Other forms of heart disease	6 (1.33)
Diseases of esophagus, stomach, and duodenum	6 (1.33)
Viral hepatitis	5 (1.11)
Benign neoplasms, except benign neuroendocrine tumors	5 (1.11)
Major depressive disorder	5 (1.11)
Tension-type headache	5 (1.11)
Cataract	5 (1.11)
Dermatitis and eczema	5 (1.11)
Dysphasia and aphasia	5 (1.11)
Congenital malformations of the circulatory system	5 (1.11)
Dizziness and giddiness	5 (1.11)
Others	174 (38.67)

Note. Some patients had more than one comorbid diseases.

in Table 4. Of those, one pair had major severity, while the other nine pairs were moderate severity. The top three drug interactions were folic acid/ phenytoin (24.90%), aspirin/ sodium valproate (19.18%), and simvastatin/ phenytoin (13.06%).

Discussion

The present study found that potential drug interaction between antiepileptic drugs and concurrent medications for comorbid diseases. Of the top 10 pairs of drug interaction, one was defined as major drug interaction and the nine pairs were moderate severity of drug interaction. These results may indicate be due to several reasons; physicians may not be knowledgeable or aware of concomitant prescribed medication which may be prescribed by other physicians; no drug interaction alert in the hospital database; or even ignorance by physicians. Additionally, it might be lack of clinical evidence of drug interaction between anti-epileptic drugs and other medications even with the new-generation anti-epileptic drugs such as perampanel[12-14]. Some anti-epileptic drugs may have drug interaction due to pharmacokinetics of enzyme inducers or inhibitors[13]. Therefore, drug interactions should be carefully considered in persons with epilepsy and even more cautious in specific populations such as elderly or pregnant women[15,16]. The present study showed that folic acid, a common drug, had the highest rate of drug interaction at 24.90% (Table 4).

A recent review of nine articles from North America (8 articles) and UK (1 article) found that arthritis was the most common comorbid disease with the prevalence of 43%, followed by hypertension (34.2%), and migraine (34.7%)[2]. Unlike the previous review, the present study

Table 2. Details of anti-epileptic drugs prescribed in persons with epilepsy (n=450)

Factors	Number (%)
Amount of anticonvulsant	
1 drug	34 (7.56)
2 drugs	229 (50.89)
3 drugs	130 (28.89)
4 drugs	42 (9.33)
≥5 drugs	15 (3.33)
List of anticonvulsant	
Sodium valproate	252 (56.00)
Phenytoin	214 (47.56)
Levetiracetam	186 (41.33)
Clonazepam	139 (30.89)
Lamotrigine	81 (18.00)
Topiramate	79 (17.56)
Carbamazepine	58 (12.89)
Phenobarbitone	46 (10.22)
Gabapentin	26 (5.78)
Perampanel	13 (2.89)
Clobazam	11 (2.44)
Diazepam	8 (1.78)
Oxcarbazepine	7 (1.56)
Lacosamide	3 (0.67)
Pregabalin	3 (0.67)
Zonisamide	2 (0.44)

Note. Some patients had received more than one anti-epileptic drugs

Table 3. Details of medications prescribed for the treatment of comorbidities in persons with epilepsy (n=450)

Factors	Number (%)
Number of medications	
1 drug	83 (18.44)
2 drugs	42 (9.33)
3 drugs	32 (7.11)
4 drugs	26 (5.78)
5 drugs	24 (5.33)
6 drugs	11 (2.44)
7 drugs	8 (1.78)
8 drugs	4 (0.89)
9 drugs	7 (1.56)
≥10 drugs	8 (1.78)
List of the medications	
Folic acid	126 (28.00)
Aspirin	84 (18.67)
Simvastatin	63 (14.00)
Vitamin B complex	61 (13.56)
Omeprazole	53 (11.78)
Atorvastatin	48 (10.67)
Amlodipine	44 (9.78)
Metformin	31 (6.89)
Amitriptyline	30 (6.67)
Baclofen	27 (6.00)
Clopidogrel	26 (5.78)
Calcium carbonate	26 (5.78)
Enalapril	25 (5.56)
Warfarin	23 (5.11)
Multivitamin	22 (4.89)
Sennosides	18 (4.00)
Glipizide	16 (3.56)
Prednisolone	15 (3.33)
Betahistine	14 (3.11)
Lorazepam	14 (3.11)
Losartan	14 (3.11)
Trihexyphenidyl	13 (2.89)
Levodopa/benserazide	13 (2.89)
Others	405 (90.00)

Note. Some patients had received more than one medications

Table 4. The 10 drug interactions between anti-epileptic drugs and other prescribed medications in persons with epilepsy

Pairs of medications	Level of severity	Details of effects	%
Folic Acid/Phenytoin	Moderate	Folic acid may potentially reduce the amount of phenytoin in the blood	24.90
Aspirin/Sodium valproate	Moderate	Aspirin may potentially increase sodium valproate in the blood	19.18
Simvastatin/Phenytoin	Moderate	Phenytoin may potentially reduce the amount of HMG-CoA reductase inhibitors (Statins) in the blood	13.06
Atorvastatin/Phenytoin	Moderate	Phenytoin may potentially reduce the amount of HMG-CoA reductase inhibitors (Statins) in the blood	9.80
Omeprazole/Phenytoin	Moderate	Omeprazole can increase the level of Phenytoin in the blood	9.80
Amlodipine/Phenytoin	Moderate	Phenytoin can reduce the level of Amlodipine in the blood	8.57
Amitriptyline/Clonazepam	Moderate	This combination can accelerate the function of the central nervous system, leading to some adversative behaviors	5.71
Warfarin/Phenytoin	Major	Phenytoin can increase the level of Warfarin in the blood, and vice versa	2.86
Warfarin/Sodium valproate	Moderate	Sodium valproate may reduce Warfarin's ability in protein pairing with the plasma	1.22
Metformin/Lamotrigine	Moderate	Lamotrigine may increase the level of Metformin in the blood	0.82

found that cardiometabolic diseases were more common in persons with epilepsy in Thailand; hypertension (16.22%), stroke (12.44%), and diabetes (12.22%). These data were compatible with the national survey from Thailand[17]. These differences of our data from the previous review may be explained by different study population as the previous review included only studies from the North America and UK[2].

There are some limitations in the present study. First, drug interactions reported in the present study defined by the application, not the clinical report. Second, there is no intervention in the present study such as therapeutic drug monitoring or treatment related with comorbid diseases[3,18-20]. Data from electronic medical records may also be incomplete or underestimated due to the retrospective nature. Finally, drug interactions between anti-epileptic drugs were not reported[21] particularly with over-the-counter medications or herbs. The outcomes of drug interactions were not evaluated in the present study. Further studies are needed to evaluate this aspect.

In conclusion, hypertension was the most common comorbid disease in persons with epilepsy. Drug interactions between anti-epileptic drugs and prescribed medications for comorbid diseases should be aware.

What is already known on this topic?

Persons with epilepsy have several comorbid diseases. There is limited data on comorbid diseases in persons with epilepsy in Thailand as well as drug interactions prescribed.

What this study adds?

Persons with epilepsy in Thailand had hypertension as the most common comorbid disease. Several severe drug interactions were prescribed in persons with epilepsy at a university hospital in Thailand.

Acknowledgements

The authors thank the Department of Medicine, Faculty of Medicine, Khon Kaen University for publication support.

Conflicts of interest

The authors declare no conflict of interest.

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