LEVETIRACETAM USE, AVAILABILITY AND KNOWLEDGE OF TOXICITY AMONG EPILEPTIC PATIENTS AND THEIR CARE GIVERS: A CROSS-SECTIONAL STUDY IN KING SALMAN ARMED FORCES HOSPITAL TABUK SAUDI ARABIA

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ABSTRACT

Background: Levetiracetam (Keppra®) is a well-known second-generation anti-epileptic drug (AED). The study was aimed to addresses Levetiracetam use, availability and knowledge of toxicity among epileptic patients and their care givers in King Salman Armed Forces Hospital Tabuk Saudi Arabia.

Methods: This cross-sectional survey was conducted in King Salman Armed Forces Hospital (KSAFH) in Tabuk city in Saudi Arabia. The study participants were epileptic patients and their care givers, selected from different outpatient departments using a convenient sampling technique. Data was collected using an Arabic self-reported questionnaire consisted of open-ended and closed-ended questions to facilitate study participants. Altogether, 381 persons answered the full questionnaire. The data were entered into SPSS version 26.0 for Windows, cleaned and managed before analysis.

Results: Participants age ranged from 18 to 63 years, with a mean 29.6 years and standard deviation 5.8 years. 47.0% (n= 179) were male and 53.0% (n= 202) female. Six out of ten participants lived in the urban area (67.7%). Majority of the participants had knowledge about seizures (96.9%). About 31.0% of the participants and/or patients had seizures (epilepsy) since more than 20 years. Nearly 28.0% participants and/or patients had family history of seizures (epilepsy). Majority of the participants had Levetiracetam at home and aware of the correct usage of it. However, about 11% of the participants felt that Levetiracetam is used to help sleep. Eight out of ten of the participants reported "Sleepiness" as the side effect of Levetiracetam (79.3%). Half of the participants reported "Headache" as the side effect of Levetiracetam. About 94.0% of the participants knew that someone could take enough Levetiracetam to harm themselves.

Conclusion: The study population used Levetiracetam, they demonstrated basic awareness of Levetiracetam use including the potential consequences of overdosing. Participants' knowledge regarding the toxicity of Levetiracetam is adequate. Special awareness programs for parents of children with epilepsy may be needed to reduce the knowledge gaps in the management of epilepsy and to ensure compliance and optimal therapeutic outcomes.

KEYWORDS

Levetiracetam, anti-epileptic drug, knowledge, use, side effects.

INTRODUCTION

Levetiracetam is a pyrrolidine derivative antiepileptic drug [1]. Clinically, Levetiracetam is used for certain types of partial, myoclonic and primary generalized tonic-clonic seizures in adults and children [2, 3]. Both the oral solution and IV formulation of Levetiracetam was initially approved by United States Food and Drug Authority (US FDA) in 1999 [4]. Antiepileptic drugs (AEDs) are relatively inexpensive but high volumes of prescriptions obviously mean that substantial savings in the medication budget can be made by switching from brand drugs to cheaper generic drugs [5]. However, in epilepsy more caution may be required because of the restricted therapeutic range of most AEDs [6].

Switching to the cheapest generic AED can provide savings in drug budgets but it overlooks the patient safety. Many generic medications can cause an unexpected side effects and may be clinically not equivalent to brand drugs [7]. The challenges and increased risks of generic medications provide an outline for organizing framework and bioequivalence studies [8]. The authorities can use this results to improve medication safety. It also helps to make informed decisions in the selection of the safest generic medications which will lead to lower medication cost especially for immunosuppressive drugs, oncology, and biological medications [9-11].

King Salman Armed Forces Hospital (KSAFH) is a military setting hospital located in the northwest region in Tabuk Saudi Arabia. The aim of this study was to assess the availability, usage, and knowledge of toxicity of oral Levetiracetam among patients attending in KSAFH. So far, however, no studies have been conducted on assessment of knowledge of toxicity of Levetiracetam in KSAFH. The results from this will be used to ensure high-quality generic drug therapy for patients at military hospitals, reduce the brand medication costs, make patients feel safe taking generic medications.

MATERIALS AND METHODS

Study Population and Study Design

This hospital-based cross-sectional study was carried out in King Salman Armed Forces Hospital in Tabuk Saudi Arabia. The epileptic

patients who willingly agreed to participate were included in the study. If epileptic patients were unable to provide informed consent, then person accompanying the patients asked to fill questionnaire and asked to provide the information about their patients. The inclusion criteria for the study participants were that participants should be adults (either gender, male or female) and who willingly agreed to participate in the study. Those who refused to participate, could not read the study questionnaire, were below 18 years of age were excluded from the study. The study period lasted from January 2019 to June 2019. Informed consent to participate in the study was obtained prior to the start of the study.

Sample Size and Sampling Procedure

The sample size for this study was calculated using Epi Info version 7 (Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA) with the following equation:

$$\text{Sample size } n = \left[\frac{\text{DEFF} * Np(1-p)}{\left[\left(\frac{d^2}{Z^2} \right) * (N-1) + p * (1-p) \right]} \right]$$

The parameters were taken as follows:

Population size (for finite population correction factor or FPC) (N): 1000000

Hypothesized % frequency of outcome factor in the population (p): 50% +/- 5

Confidence limits as % of 100 (absolute +/- %) (d): 5%
Design effect (for cluster surveys-DEFF): 1

The sample size calculated from the above formula was approximately 384. A convenient sampling method was used to carry out this survey. Participants were requested to answer questionnaires. A total of 500 questionnaires were distributed. Three hundred eighty-one participants willingly and voluntarily participated in the study.

INCLUSION-EXCLUSION CRITERIA

The inclusion criteria are as follows:

- Epileptic Patient:

1. Able to read and write
2. Able to give written consent
3. Taking treatment at KSFAH hospital
4. Any gender
5. Any nationality

• Person accompanying epileptic patient if the patient is not able to read and write

The exclusion criteria are as follows:

- Not able to read and write
- Having any disability/illness (physical or mental)
- Outside the study period
- Not willing to participate in the study

Study Questionnaire

A one page, 21 item questionnaire was developed by the two subject experts with extensive literature review. The questionnaire included both multiple choice and open ended questions related to: (1) demographic data of the participants, (2) prescribed dose of Levetiracetam, (3) availability at home and usage of Levetiracetam, (4) knowledge of side effects, (5) knowledge of potential for harm or lethality in overdose, and (6) knowledge of quantity of drug to cause harm or death. The study questionnaire was forward and backward translated from English into Arabic with the help of a bilingual translator. The pretested and validated study instrument was first pilot-tested on 20 participants and then administered to the study participants who fulfilled the inclusion criteria by research assistants. The anonymity of the respondents is assured.

Data Management and Statistical Analysis

All questionnaires were checked manually, and 100% filled questionnaires were included in the analysis. All the completed questionnaires were entered into SPSS Statistics version 26.0 (IBM; Chicago, IL, USA) for data analysis. Descriptive statistics and univariate analysis were performed (Pearson's Chi-squared tests or Fisher's exact tests were used for categorical variables, while Student's t-tests were utilized to assess the association between continuous variables). A p-value less than 0.05 was considered statistically significance.

RESULTS

Of the 500 questionnaires distributed, three hundred eighty-one participants responded to the study for an overall response rate of 76.2%. Data from 381 respondents was considered for the final analysis. Cronbach's alpha test was conducted to test of internal consistency and reliability the study questionnaire. It was testified that the reliability of this questionnaire was acceptable, with 0.816 as the reliability coefficient.

Socio-demographic characteristics of the study participants

Table 1 shows some selected socio-demographic characteristics of the study participants. Age ranged from 18 to 63 years, with a mean 29.6 years and standard deviation 5.8 years. 47.0% (n= 179) were male and 53.0% (n= 202) female. Six out of ten participants lived in the urban area (67.7%). More than half of the participants had a university degree (57.0%), while 120 (32.0%) had a high school education.

Table1: Socio-demographic characteristics of the study participants (n=381)

Characteristics	Category	Frequency	Percentage
Gender	Male	178	46.7
	Female	203	53.3
Age	18-21 years	72	18.9
	22-30 years	166	43.6
	31-40 years	103	27.0
	41-50 years	29	7.6
	More than 50 years	11	2.9
Place of residence	Rural	123	32.3
	Urban	258	67.7
Highest academic qualification	Primary	15	3.9
	Intermediate	27	7.1
	High School	122	32.0
	Bachelors	176	46.2
	Master/Doctors	41	10.8

Employment status	Student	73	19.2
	Employed	215	56.4
	Unemployed	41	10.8
	Others	52	13.6

Seizures (epilepsy) and its related particulars

Table 2 describes the responses of the participants towards seizures (epilepsy). Majority of the participants had heard about the disease seizures (96.9%). About 31.0% of the participants and/or patients had seizures (epilepsy) since more than 20 years. Six out of ten participants and/or patients had breakthrough seizure in the last year. Approximately 28.0% participants and/or patients had family history of seizures (epilepsy).

Table 2: Seizures (epilepsy) and its related particulars (n=381)

Questions	Category	Frequency	Percentage
Have you heard about the disease seizures (epilepsy)?	Yes	369	96.9
	No	12	3.1
Do you have seizures (epilepsy)?	Yes	107	28.1
	No	274	71.9
Duration of seizures (epilepsy) you/your patient have	For the past 5 years	129	33.9
	For the past 6-10 years	57	15.0
	For the past 15-20 years	72	18.9
	More than 20 years	118	31.0
	Don't know	5	1.3
Do you/your patient had breakthrough seizure in the last year?	Yes	241	63.3
	No	136	35.7
	Don't know	4	1.0
Do you/your patient had visited emergency room for breakthrough seizure in the last year?	Yes	236	61.9
	No	137	36.0
	Don't know	8	2.1
Do you/your patient had hospital admission breakthrough seizure in the last year?	Yes	191	50.1
	No	185	48.6
	Don't know	5	1.3
Do you have family history of seizures (epilepsy)?	Yes	105	27.6
	No	269	70.6
	Don't know	7	1.8

Levetiracetam availability, use, and therapeutic indications and knowledge of its toxicity Table 3 shows Levetiracetam availability, use, and therapeutic indications and knowledge of its toxicity.

Majority of the participants had Levetiracetam at home and aware of the correct usage of it. However, about 11% of the participants felt that Levetiracetam is used to help sleep. Eight out of ten of the participants reported "Sleepiness" as the side effect of Levetiracetam (79.3%). Half of the participants reported "Headache" as the side effect of

Levetiracetam. About 94.0% of the participants knew that someone could take enough Levetiracetam to harm themselves.

Table 3: Levetiracetam availability, use, and therapeutic indications and knowledge of its toxicity (n=381)

Questions	Category	Frequency	Percentage
Levetiracetam is used to treat (choose correct answer(s)) (multiple responses)	Seizures (epilepsy)	315	82.7
	Fever	12	3.1
	Cold and flu	17	4.5
	Vomiting/sickness	22	5.8
	Infections	5	1.3
	Pain/headaches	36	9.4
	To help sleep	43	11.3
Do you have Levetiracetam at home?	Don't know	18	4.7
	Yes	352	92.4
	No	17	4.5
Do you/your patient had Levetiracetam Dosage	Don't know	12	3.1
	120 mg	23	6.0
	150 mg	33	8.7
	250 mg	55	14.4
	750 mg	206	54.1
	1000 mg	42	11.0
	Don't know	22	5.8
Do you/your patient had taken Levetiracetam within the last year?	Yes	357	93.7
	No	11	2.9
	Don't know	13	3.4
Side effects (problems) from taking Levetiracetam are (multiple responses)	Sleepiness	302	79.3
	Weakness	123	32.3
	Dizziness	150	39.4
	Double vision	75	19.7
	Aggression	105	27.6
	Loss of balance or coordination	126	33.1
	Headache	209	54.9
	Loss of appetite	75	19.7
	Vomiting	40	10.5
	Diarrhoea	53	13.9
	Constipation	62	16.3
	Fever	34	8.9
	Others	132	34.6
	Don't know	12	3.1
Could someone take enough Levetiracetam to harm themselves?	Yes	358	94.0
	No	8	2.1
	Don't know	15	3.9
If yes how many tablets in one go (each tablet is 500 mg)	1 tablet	6	1.6
	2 tablets	9	2.4
	3 or more tablets	354	92.9
	Don't know	12	3.1

DISCUSSION

Epilepsy is the most common neurological disease that affects around 50 million people worldwide [12]. Levetiracetam is a broad-spectrum antiepileptic drug with a unique mechanism of action. AEDs are strong agents that can cause numerous adverse reactions and drug-drug interactions [13-15]. This survey is aimed to determine the usage, availability and knowledge of toxicity of Levetiracetam among the

patients. The primary findings of this study included that (1) Majority of the patients used Levetiracetam (2) Nine out of ten participants had Levetiracetam at home, and (3) Sleepiness, headache, dizziness, loss of balance or coordination and weakness.

The present study revealed that majority of the participants had previously heard about seizure (epilepsy). This finding is consistent with the education levels of this study population and previously published studies [16-18]. This study determined that one out of three patients had seizure (epilepsy) for the past 5 years. A similar pattern of response was observed in studies conducted in other countries [19]. Furthermore, this study reported that six out of ten patients had breakthrough seizure in the last year and visited emergency department. This finding agrees with results from previous studies, which reported approximately 60 percent of the patients had seizure in the past year [20].

The present study showed that one out of four patients had positive family history of seizure. This result is in line with other studies that reported that 25 percent epileptic patients have positive family history of epilepsy [21, 22]. The present study confirms that majority of the participants knew that Levetiracetam is used to treat seizures (epilepsy). This result supports the results of other studies showing that patients and their care givers knew about the usage of Levetiracetam. Surprisingly, a significant number of the participants, despite their educational status and familiarity with epilepsy, still believe that Levetiracetam is used to help sleep, pain/headaches, cold and flu [23].

In this study most of the participants reported sleepiness as the most common side effect of Levetiracetam, this result is in line with other studies conducted in epileptic patients [24, 25]. However, there were not reported any life-threatening side effects. Headache was the second most common side effect reported in this study. Other studies have found that the similar observation [15]. Finally, with regard to whether participants believed Levetiracetam could harm or kill, majority of them were aware about the toxicity of Levetiracetam. About 28 percent participants were reported aggression as one of the side effect of Levetiracetam. Some studies have reported that Levetiracetam has psychosocial and behavioral side effects in children and adults [16, 26].

Strengths and Limitations of the Study

The strength of this research is that this analysis will provide liaison between the medical services and food drug authorities and advise the central pharmacy and therapeutic committee on the substitution a generic for a brand medication. However, as this is self-reported questionnaire, we must rely on respondents' honesty and memory recall.

Conclusion and Recommendations

Levetiracetam is commonly used among epileptic patients and many patients and their care givers are unaware of its side effects. The findings of this study showed that participants' knowledge regarding the toxicity of Levetiracetam is adequate. Also, it is important to improve patients' knowledge, attitudes and practices regarding Levetiracetam use to reduce the misconceptions and misguided expectations contributing to inappropriate anti-epileptic drug use. Therefore, health professional practice should play a major role in people's awareness of the appropriate use of anti-epileptic drugs.

Ethics approval and consent to participate

Before beginning the data collection process, informed consent was taken from each participant. On the top of the first page of each questionnaire a brief note also stated indicating voluntary participation. Privacy and confidentiality of the participants were maintained throughout the study period. The ethical approval of this study was obtained from the local research and ethics committee at King Salman Armed Forces Hospital.

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

OA and FA wrote the research proposal. OA, FA and NS analysed the

data, interpreted the results and wrote the manuscripts. OA and FA contributed to the data-gathering process, supported the necessary logistics and accepted the manuscript. All writers decided to have the manuscript submitted for publication.

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