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Research Article

THE OFF-LABEL USE OF CARBAMAZEPINE IN INDONESIA

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ABSTRACT

Objective:. In Indonesia, carbamazepine was approved by The National Agency of Drugs And Foods Controls for the prophylaxis of lithium unresponsive manic-depressive disorders, all types of epilepsy (except for petit mal), and trigeminal neuralgia. This study was conducted to determine the off-label use of carbamazepine in Indonesia.

Methods: This research is a nonexperimental descriptive study with a cross-sectional method. Data collection retrospectively by taking all patients that were prescribed carbamazepine in 2014. Data were obtained from four general hospitals in Yogyakarta. The off-label use of carbamazepine was defined a prescribing of carbamazepine outside the indication that approved by The National Agency for Drugs And Foods Controls of Republic of Indonesia (NA-DFC).

Results: The use of carbamazepine in 2014 were 704 prescriptions, and on 251 (35.6%) of them were off-label drug use. The off-label use of carbamazepine were 149 prescriptions (59.4%) for neuropathic pain, 83 prescriptions (33.0%) for nociceptive pain, and 19 prescriptions (7.6%) for other indications.

Conclusion: The mostly off-label use of carbamazepine in Indonesia was in neuropathic pain with low evidence. Further research to study the efficacy and the risk of off-label use of carbamazepine may be an essential step toward defining the potential for such purpose.

Keywords: Anticonvulsant, Carbamazepine, Prescription, Off-label, Neuropathic pain

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INTRODUCTION

Off-label prescribing refers to understanding the use of drugs that are officially registered with the indications, dosage, patient age, and route of administration that is different from the description is written in the product information [1]. The off-label drug use is prevalent in almost all the world. A study in Germany from 2003 to 2006 found that off-label drugs use was as much as 40.2% [2]. Other data from Australia found 60% of off-label prescribing in 9 children's hospital, and 26% off-label prescribing in outpatients at an academic hospital in Sydney [3]. In Brazil, prescribing of an off-label drug was found in 86% of prescriptions (at least one off-label drug use) [4].

A class of drugs often prescribed off-label was medications that act on the nervous system. A study revealed that the highest prevalence of off-label drug use was anticonvulsants (74%) and the second was antipsychotics (60%) [5]. One of the off-label uses of anticonvulsants is for neuropathic pain therapy. Carbamazepine is an anticonvulsant that was first investigated for neuropathic pain, especially trigeminal neuralgia [6]. Almost all anticonvulsants have anti-pain effect in some types of neuropathic pain [7,8]. An opinion stated that the treatment of chronic neuropathic pain gained excellent results when given anticonvulsants, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors. The recommended anticonvulsants were gabapentin, pregabalin, carbamazepine, and oxcarbazepine [9].

Carbamazepine (5H-dibenz [b, f] azepine-5-carboxamide) was introduced in the 60s and prescribed as an antiepileptic. Carbamazepine is also used for neuropathic pain and psychiatric diseases. Structurally, carbamazepine is a derivative amino benzyl similar to tricyclic antidepressants. Extensively metabolized in the liver and only 1% is excreted in the form of the parent compound. Its active metabolite, carbamazepine-10,11-epoxide have anticonvulsant effects similar to carbamazepine [10].

The mechanisms of carbamazepine for neuropathic pain is expected for its ability to block sodium channels, thereby reducing the excitability of damaged nerve cells [11,12]. Carbamazepine is also expected to affect nociceptive pain by intervention in γ-aminobutyric acid (GABA)-ergic and somatostatinergic. Another mechanism with low evidence-based is by blocking calcium channels and excitatory amino acids [8,13]. Several studies on the use of carbamazepine for neuropathic pain have been summarized in a systematic review conducted by Wiffen *et al*. In that review mentioned some studies of the use of carbamazepine on trigeminal neuralgia, painful diabetic neuropathy, and post-stroke pain [14].

FDA warning for the use of carbamazepine: All patients who are currently or are starting to get carbamazepine should be monitored for important changes in behavior that may indicate the appearance or worsening of suicidal thoughts or depression. The frequent adverse drug reaction (ADR) of carbamazepine is sedation, headache, diplopia, blurred vision, rash, indigestion, ataxia, tremors, impotence, hyponatremia, and neutropenia. The seriously ADR is allergic skin rash, hepatotoxicity, and Stevens-Johnson syndrome [15].

In Indonesia, in 2014, distribution license carbamazepine approved by NA-DFC was the indication of prophylaxis of manic-depressive diseases unresponsive to lithium, antiepileptics, epilepsy all kinds, except petit mal, and trigeminal neuralgia. In the early year's carbamazepine entered Indonesia, trigeminal neuralgia is not listed on the official indications. There are no new indications of a license issued by NA-DFC up to this writing. Data on the off-label use of

carbamazepine in Indonesia has not established yet. This study was conducted to determine the prevalence and the indication of the off-label use of carbamazepine in Indonesia.

METHODS

Design of study and sampling

Data obtained from carbamazepine prescription during 2014. Data indication obtained from medical records of patients who received carbamazepine. Medical records that cannot be traced were excluded from this study. The population in this study was all patients who receive carbamazepine in 2014. This research is a nonexperimental descriptive study with a cross-sectional method. Data were collected retrospectively.

Setting

This study was conducted in several general hospitals, such as Dr. Sardjito Central General Hospital, UGM (Universitas Gadjah Mada) Academic Hospital, PKU Muhammadiyah Hospital, and Bethesda Hospital. All public hospitals are located in the province of Jogjakarta, which have a neurological disease poly. The Dr. Sardjito Central General Hospital is a central public hospital that serves as a referral hospital in Jogjakarta and the surrounding area. UGM Academic Hospital represents an academic hospital. PKU Muhammadiyah Hospital and Bethesda Hospital represent private hospitals.

Data analysis

Identification of the use of carbamazepine done by checking the diagnoses listed in medical records at the date of carbamazepine prescription. The off-label use of carbamazepine was defined a prescribing of carbamazepine outside the indication that approved by NA-DFC.

Ethical approval

The study was approved by the Medical and Health Research Ethics Committee Faculty of Medicine Universitas Gadjah Mada - Dr. Sardjito Public Hospital (Ref: KE/FK/525/EC/2015).

RESULTS

From this study, the number of carbamazepine use during 2014 from four hospitals in Yogyakarta is 704 prescriptions. We found 453 (64.4%) prescribed according to NA-DFC Indonesia, indication registered in 2014, 251 (35.6%) are prescribing off-label.

Patients characteristics

The characteristics of patients receiving an off-label prescription of carbamazepine can be seen in Table 1. Female patients were more likely to receive off-label prescriptions of carbamazepine (56.2%). Patients 51–60 years are the most patients get off-label prescription of carbamazepine. It is because the most indicative of the off-label use of carbamazepine is on neuropathic pain with various causes. Neuropathic pain is common in patients over 50 years when associated with degenerative diseases.

A total of 251 off-label prescriptions included 149 prescriptions (59.4%) for neuropathic pain, 83 prescriptions (33.0%) for nociceptive pain, and 19 prescriptions (7.6%) for other indications. Indications for neuropathic pain use of carbamazepine are summarized in Table 2.

The others indication of carbamazepine uses in 2014 is summarized in Table 3.

DISCUSSION

Carbamazepine for neuropathic pain

From Table 2, it is known that the most use of carbamazepine outside of the official indication was for neuropathic pain, which amounted to 149 (59.4%). Five major indications of carbamazepine prescription in neuropathy pain are for stroke 35 (23.5%), painful diabetic neuropathy 25 (16.8%), cancer pain 18 (12.1%), herniated nucleus pulposus 12 (8.0%), and traumatic cerebral edema 8 (5.4%).

Table 1: Demographic and characteristics of patients (N=251)

Patient characteristics	N (%)	Mean (SD)
Gender		
Male	110 (43.8)	
Female	141 (56.2)	
Age		
0–10s	5 (2.0)	54.1 (15.1)
11–20s	2 (0.8)	
21–30s	12 (4.8)	
31–40s	18 (7.2)	
41–50s	50 (19.9)	
51–60s	77 (30.7)	
61–70s	53 (21.1)	
71–80s	32 (12.7)	
81–90s	2 (0.8)	
Physician specialty		
Neurologist	221 (88.0)	
Neurosurgeon	5 (2.0)	
Pediatricians	4 (1.6)	
Others specialty	21 (8.4)	
Total	251	

SD: Standard deviation

Table 2: The indications for neuropathic pain use of carbamazepine in 2014

No	Indication	Amount (%)
	Neuropathic pain	
1	Stroke	35 (23.5)
2	Diabetic neuropathy	25 (16.8)
3	Cancer pain	18 (12.1)
4	Herniated nucleus pulposus	12 (8.0)
5	Traumatic cerebral edema	8 (5.4)
6	Herpes zoster	7 (4.7)
7	Post-operative	6 (4.0)
8	Polyneuropathy	6 (4.0)
9	Low back pain	5 (3.4)
10	Neuropathic syndrome	5 (3.4)
11	Vertigo	5 (3.4)
12	Myalgia	5 (3.4)
13	Ischialgia	2 (1.3)
14	Fibromyalgia	2 (1.3)
15	Cervical syndrome	2 (1.3)
16	Paraparesis	2 (1.3)
17	Adhesive capsulitis of shoulder	1 (0.7)
18	Trigger finger	1 (0.7)
19	Fracture	1 (0.7)
20	Tetraparesis	1 (0.7)
	Total	149 (100)

Carbamazepine is the first line in the treatment of trigeminal neuralgia. Many studies have been doing the use of carbamazepine for trigeminal neuralgia, both efficacy and safety studies [11,16,17]. The use of carbamazepine for other neuropathic pain indications has not been registered, and there is no strong evidence. This study found that carbamazepine is used for post-stroke pain, painful diabetic neuropathy, a neuropathic pain of cancer, and others. Research the use of carbamazepine for neuropathic pain other than trigeminal neuralgia already been done with evidence level low and very low [12,13,16]. Only one study assessed the efficacy of carbamazepine in the central post-stroke pain. The study conducted on 15 patients with central post-stroke pain. The results obtained are 5 of 14 patients experienced a decrease in pain but was not statistically significant compared to placebo [13]. Study on the use of carbamazepine for painful diabetic neuropathy was also conducted. Two studies compared carbamazepine with placebo, which carbamazepine showed positive results. One study compared carbamazepine with the combination of nortriptyline and fluphenazine, no significant difference between two groups. Another study comparing carbamazepine with venlafaxine in

Table 3: The others used of carbamazepine in 2014

No	Indication	Amount (%)
	Nociceptive pain	
1	Personal history of the circulatory system	30 (36.1)
2	Cephalgia	15 (18.1)
3	Pain in joint	6 (7.2)
4	Osteoarthritis	5 (6.0)
5	Parkinson	3 (3.6)
6	Hemodialysis/renal	2 (2.4)
7	Bell palsy	2 (2.4)
8	Observation suspect disease and condition	2 (2.4)
9	Congestive heart failure	2 (2.4)
10	Cerebral palsy	2 (2.4)
11	Canal stenosis	2 (2.4)
12	Asthma bronchial attack	2 (2.4)
13	Hyponatremia, hypokalemia	2 (2.4)
14	Hypertension, hyperlipid	1 (1.2)
15	Chronic obstructive pulmonary	1 (1.2)
16	Abnormality of heartbeat	1 (1.2)
17	Chest pain	1 (1.2)
18	Periodic limb movement disorder	1 (1.2)
19	Abdomen pain with vomiting	1 (1.2)
20	Impaksi, afeksi	1 (1.2)
21	Dyspepsia	1 (1.2)
	Subtotal	83 (100)
	Psychosis	
22	Schizophrenia	7 (36.8)
23	Personal history of other mental and behavioral disorder	1 (5.3)
24	Insomnia	1 (5.3)
	Infection	
25	Encephalitis	6 (31.6)
26	Pharyngitis, stomatitis	2 (10.5)
27	Cellulitis	1 (5.3)
28	Cytomegalovirus	1 (5.3)
Subtotal		19 (100)

patients with painful diabetic neuropathy that venlafaxine show larger mean effect [18-21]. The newer study about the use of carbamazepine for a treatment of painful diabetic neuropathy was conducted by Maheshwary *et al.* This study shows that carbamazepine reduced mean pain severity and mean pain interference scores, improved quality of life, and good tolerability when prescribed for 12 weeks to an adult diabetic patient [22]. The study of the use of carbamazepine in preventing postherpetic neuralgia following acute herpes zoster has been done with the result carbamazepine was less effective than prednisolone [16].

The mechanisms of carbamazepine for neuropathic pain is by blocking the sodium channels can reduce the excitability of nerve cells. In neuropathic pain, both peripheral and central have the characteristics of their hyperexcitability of the nerve cells if these nerve cells were damaged. Hyperexcitability of nerve cells caused by damage to nerve cells with a variety of reasons. In peripheral neuropathic pain, the nerve endings are damaged causing spontaneous pain and increase in seizure activity, partly due to the rise in sodium channel expression in the organ. In central neuropathic pain, spontaneous pain and rising allodynia can also be explained by the mechanism of neuronal hyperexcitability. Peripheral hyperexcitability occurs because of a series of molecular changes in the peripheral nociceptors, dorsal root ganglia, dorsal horn of the spinal cord and brain. These changes include increased activity of glutamate receptor, changes inhibition of GABAergic, changes in calcium influx into the cell. This mechanism has some similarities with the mechanisms involved in epilepsy, and thus many anticonvulsants can use as an anti-neuropathic pain [7,8,14]. The use of carbamazepine in neuropathic pain has been tested in the clinic, but it is rarely used as a first-line therapy, except for trigeminal neuralgia. Some doctors still prescribe carbamazepine because of it still effective in some people. Further studies are still needed [23]. In MS and SUM Hospital, SOA University, Bhubaneswar, Odisha, there were 52 (7.2%) prescriptions of carbamazepine for the management of neuropathic pain (from 721 anticonvulsants prescriptions for neuropathic pain) [24].

Carbamazepine for nociceptive pain

The second use of carbamazepine was for nociceptive pain, among others on cephalgia, osteoarthritis, pain in the joint, and others. The mechanism of nociceptive pain is estimated to the ability of carbamazepine to intervene on GABAergic and somatostatinergic. Other mechanisms, which low evidence, were by blocking calcium channels and excitatory amino acids. There is no evidence found in the use of carbamazepine for nociceptive pain [25,26].

Carbamazepine for psychosis

From this study, there is the use of carbamazepine in cases of psychosis, i.e., for schizophrenia, personal history of other mental and behavioral disorder, and insomnia. Carbamazepine is already approved for use on a manic-depressive who are not responsive to lithium prophylaxis therapy and manic-depressive. Indications other psychoses have not been registered, some research on the efficacy and safety has been done. The use of carbamazepine for schizophrenia has lack efficacy, for the mental and behavioral disorder, only two small placebo-controlled trials have been done [12,27-29]. The common ADRs of anticonvulsant were nausea, dizziness, and drowsiness. The chronic use of anticonvulsants has a significant risk of developing osteoporosis and anemia [24,30].

Other indications

Another use of carbamazepine obtained in this study is in some infectious diseases such as encephalitis, cytomegalovirus (CMV), cellulitis, pharyngitis, and stomatitis. On encephalitis and CMV administration of carbamazepine are expected to febrile seizures, while at cellulitis and pharyngitis possibly associated pain while at thought to be related abdominal cramps. It is still necessary searches and further research.

Prescribers

Carbamazepine at the four hospitals was used in this study the most prescribed by a neurologist, followed by neurosurgeon, pediatricians, and other medical specialists. It is according to research from Onyenwenyi [31]. She mentions in the theoretical framework that physician characteristics influence the decision-making. The factors that influence are physician age/recency of professional training, gender, specialty, interpersonal relationship with the patient, and interaction with the medical profession and the healthcare system [31].

Limitation

The limitation of this study is just a retrospective study, so it could not determine the drug-related problem if the problem does not write in the medical record. The researcher cannot meet the physicians, so the researcher could not confirm some data. The conclusion of this study only based on the written in the medical record, may not be generalizable to another country. However, the findings have important implication for government and future research must be done on the efficacy the off-label use of carbamazepine.

CONCLUSIONS

The mostly off-label use of carbamazepine in Indonesia was for neuropathic pain with low evidence. Further research to study the efficacy and the risk of off-label use of carbamazepine may be an essential step toward defining the potential for such purpose.

AUTHORS' CONTRIBUTIONS

All authors contributed to all of the writing process of this article.

COMPETING INTERESTS

There is no conflict of interest

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