An overview of the use of Carbamazepine at PKU Muhammadiyah Hospital Yogyakarta

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ABSTRACT

Carbamazepine is often used for indications other than epilepsy. In Indonesia, carbamazepine is registered for prophylaxis for lithium-responsive manic depressive disease, antiepilepsy, epilepsy of all types (except petit mal), and trigeminal neuralgia. This research aimed to describe the use of carbamazepine at PKU Muhammadiyah Hospital Yogyakarta. This was an observational study with a cross-sectional design. The data were taken retrospectively from the medical records of patients who received carbamazepine during 2014. The use of carbamazepine included 494 prescriptions given to 117 patients. The physician who most prescribed carbamazepine was a neurologist (63.04%). The most appropriate use of carbamazepine following the National Agency for Drugs And Foods Controls of Republic of Indonesia (NA-DFC) was for epilepsy (34.19%), followed by trigeminal neuralgia (6.84%) and bipolar disorder (4.27%). The most off-label use was in cases of stroke (7.69%), followed by diabetic neuropathic pain, herniated nucleus pulposus, and cephalgia (all 3.42%). Evidence found for the off-label use of carbamazepine was in diabetic neuropathic pain and neuropathic pain post-stroke (24.53%). The use of carbamazepine at PKU Muhammadiyah Hospital is mostly on-label, with some off-label use. The off-label use of carbamazepine (24.53%) has strong evidence, while some use has a lack of scientific support or no evidence at all.

INTRODUCTION

Carbamazepine is a first-generation anticonvulsant. The antiepileptic effect is thought to originate from the inactivation of Na⁺ channels. Because of this mechanism, carbamazepine was the first anticonvulsant to be studied to relieve pain (Backonja, 2000).

Some studies suggest that carbamazepine can reduce diabetic neuropathic pain and paroxysmal attacks on trigeminal neuralgia (Backonja, 2000; Sidhu and Sadhotra, 2016). In Indonesia in 2014, carbamazepine was registered by the National Agency for Drugs and Foods Controls of Republic of Indonesia (NA-DFC) for indications of lithium prophylaxis of non-responsive manic depressive disease, epilepsy of all types (except petit mal), trigeminal neuralgia, and prophylaxis in manic depressive. There is no new indication registered by NA-DFC.

Carbamazepine is interesting to study because it is widely used in Indonesia, but there are no data...
Regarding the efficacy and safety of the use of carbamazepine. Some side effects of carbamazepine are severe, such as a decrease in blood counts and platelet counts, liver failure, and Steven Johnson syndrome; moreover, is a known teratogen. The most common side effects are drowsiness, weakness, nausea, and vomiting. Thus, the administration of carbamazepine must be monitored for blood counts and therapeutic drug monitoring (TDM). TDM is recommended because carbamazepine has a narrow therapeutic index.

This research aimed to obtain an overview of carbamazepine use at PKU Muhammadiyah Hospital in Yogyakarta. Based on this description, we hope that we can study the efficacy and safety of carbamazepine use, and further research can be done.

METHOD

Study design and sampling
This research was a descriptive observational study using a cross-sectional method. The data were collected retrospectively. The data on carbamazepine use were taken from use in 2014. The indications of carbamazepine use were seen in patients medical records. Unread medical records were excluded from this study.

Setting
This study was conducted at PKU Muhammadiyah Yogyakarta Hospital in October-December 2015.

Data analysis
The percentage use of carbamazepine was determined by calculating the amount of usage divided by total usage. On-label use was defined as the use of carbamazepine that prescribing following the approval by NA-DFC. Off-label use was defined as the use of carbamazepine different from the distribution permit.

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 AND DISCUSSION

In 2014, 494 prescriptions at PKU Muhammadiyah Hospital in Yogyakarta were given to 117 patients. The demographic data and patient characteristics are listed in Table 1.

Table 1 shows that female patients received more prescriptions for carbamazepine than male patients. The largest group of patients who received carbamazepine prescriptions were in the range of 46-55 years. The physicians that mostly prescribed carbamazepine were neurologists. This is easy to understand because carbamazepine is an anticonvulsant and works on the nervous system.

The use of carbamazepine
Throughout 2014, 117 patients received a carbamazepine prescription with a diagnosis, as shown in Table 2. From these data, it was known that 45.30% of carbamazepine was prescribed off-label. The most extensive prescription of carbamazepine is for epilepsy, followed by stroke and trigeminal neuralgia. For epilepsy and trigeminal neuralgia, the use of carbamazepine is under the carbamazepine distribution permit in Indonesia (on-label use). The purpose of carbamazepine for neuropathic pain in stroke is classified as off-label usage.

The on-label use of carbamazepine
NA-DFC registers the distribution of carbamazepine in Indonesia for indications of prophylaxis of non-responsive manic depressive disease, epilepsy of all types (except petit mal), and trigeminal neuralgia. At PKU Muhammadiyah Yogyakarta Hospital, the highest use of carbamazepine was for epilepsy (34.19%), followed by trigeminal neuralgia, bipolar, and manic depression. Carbamazepine is an antiepileptic that works by inhibiting Na+ channels. Carbamazepine is first-line therapy for focal seizures and alternative treatment for generalised tonic-clonic seizures (National Institute for Health and Care Excellence, 2013). This mechanism also causes carbamazepine to have an anti-pain effect. Carbamazepine was first tested on trigeminal neuralgia, and until now it is first-line therapy for trigeminal neuralgia. Some studies use different doses with different durations. The maximum dosage according to the FDA is 1200 mg/day (Gupta et al., 2005; Cruccu et al., 2008; McQuay et al., 1995), while the EURO group allows up to 1800 mg/day and is given for 4-6 months (Vargas-Espinosa et al., 2012; Wiffen et al., 2011).

In this study, the use of carbamazepine in trigeminal neuralgia was administered at a dose of 2 x 200 mg with an average duration of 10 days. The use of carbamazepine for manic depression, including bipolar disorder, was estimated based on the intracellular mechanism. Effects as a mood stabiliser are determined by several mechanisms including reducing dopamine breakdown, raising GABA levels through multiple actions in synthesis and degradation, modulation of other neurotransmitters, Na+ channel blockade, extrahypothalamic neuropeptides, second messenger systems,
Table 1: Demographics and patient characteristics

| Patient Characteristics | N (%)   | Mean (S.D.) |
|-------------------------|---------|-------------|
| **Gender**              |         |             |
| Male                    | 50 (42.73%) |             |
| Female                  | 67 (57.27%) |             |
| **Age**                 |         |             |
| 5yo-15 yo               | 5 (4.35%)  |             |
| 16yo-25yo               | 12 (10.14%) |             |
| 26yo-35yo               | 15 (13.04%) |             |
| 36yo-45yo               | 19 (15.94%) |             |
| 46yo-55yo               | 22 (18.84%) | 47.92 (1.97) |
| 56yo-65yo               | 19 (15.94%) |             |
| 66yo-75yo               | 13 (11.60%) |             |
| 76yo-85yo               | 10 (8.70%)  |             |
| 86yo-95yo               | 2 (1.70%)   |             |
| **The Prescription Physicians** |         |             |
| General practitioners   | 15 (13.04%) |             |
| Neurologist             | 74 (63.04%) |             |
| Internist               | 5 (4.35%)   |             |
| Neurosurgeons           | 13 (10.87%) |             |
| Others                  | 10 (8.70%)  |             |
| **Total N**             | 117      |             |
Table 2: The Indications Use of Carbamazepine

| No | The on-label use of carbamazepine                                      | N (%) | Percentage (%) |
|----|------------------------------------------------------------------------|-------|----------------|
| 1  | Epilepsy                                                               | 40    | 34.19          |
| 2  | Trigeminal Neuralgia                                                   | 8     | 6.84           |
| 3  | Bipolar affective disorder, current episode mixed                      | 5     | 4.27           |
| 4  | Manic Depression                                                       | 3     | 2.56           |
| 5  | Seizure in hydrocephalus                                              | 2     | 1.71           |
| 6  | Traumatic cerebral oedema                                              | 2     | 1.71           |
| 7  | Seizure in stroke                                                      | 1     | 0.85           |
| 8  | Encephalitis dan encephalomyelitis                                     | 1     | 0.85           |
| 9  | Myoclonus                                                              | 1     | 0.85           |
| 10 | Benign neoplasm: brain supratentorial, Hydrocephalus                   | 1     | 0.85           |
|    | **Total on label use**                                                 | **64**| **54.70**      |

| No | The off-label use of carbamazepine                                      | N (%) | Percentage (%) |
|----|------------------------------------------------------------------------|-------|----------------|
| 1  | Stroke                                                                 | 9     | 7.69           |
| 2  | Nervous system                                                         | 5     | 4.27           |
| 3  | Diabetic neuropathy                                                    | 4     | 3.42           |
| 4  | Cephalgia                                                              | 4     | 3.42           |
| 5  | HNP (Herniated Nucleus Pulposus)                                       | 4     | 3.42           |
| 6  | Herpes zoster                                                          | 3     | 2.56           |
| 7  | Pain in joint                                                          | 3     | 2.56           |
| 8  | CHF (Congestive Heart Failure)                                         | 3     | 2.56           |
| 9  | Ischialgia                                                             | 2     | 1.71           |
| 10 | Personal history of diseases of the circulatory System                 | 2     | 1.71           |
| 11 | Polyneuropathy                                                         | 2     | 1.71           |
| 12 | Schizophrenia                                                          | 1     | 0.85           |
| 13 | Parkinson                                                              | 1     | 0.85           |
| 14 | LBP (Low Back Pain)                                                    | 1     | 0.85           |
| 15 | Kidney disease                                                         | 1     | 0.85           |
| 16 | Carpal tunnel syndrome                                                 | 1     | 0.85           |
| 17 | Myalgia                                                                | 1     | 0.85           |
| 18 | Acquired absence of leg above the knee                                 | 1     | 0.85           |
| 19 | Observe for other suspect diseases and condition                       | 1     | 0.85           |
| 20 | Tumour                                                                 | 1     | 0.85           |
| 21 | Mononeuropathy                                                         | 1     | 0.85           |
| 22 | Bells palsy                                                            | 1     | 0.85           |
| 23 | Others                                                                 | 1     | 0.85           |
|    | **Total Off-label use**                                                | **53**| **45.30**      |
|    | **TOTAL**                                                              | **117**| **100**        |
| No | Author | Title | Methods | Result-Conclusion |
|----|--------|-------|---------|-------------------|
| 1. | (Leijon and Boivie, 1989). | Central post-stroke pain—a controlled trial of amitriptyline and carbamazepine | The study compared carbamazepine and amitriptyline in central post-stroke neuropathic pain. A total of 15 patients were divided into two groups. Carbamazepine and amitriptyline were given for four weeks with a 7-day wash-out period. The dose of carbamazepine was 800 mg, and the dose of amitriptyline was 75 mg, reached on the 6th and 18th days. The pain was measured by rating pain daily, and depression was measured by the Comprehensive Psychopathological Rating Scale (CPRS). There was one patient who discontinued treatment on day 25 because of drug interactions. | The results of the study in central post-stroke neuropathic pain patients showed that 5 out of 14 patients had decreased pain with carbamazepine therapy, but not statistically significantly different compared to placebo. |
| 2. | (Gómez-Pérez et al., 1996). | Nortriptyline-fluphenazine vs carbamazepine in the symptomatic treatment of diabetic neuropathy. | This study compared the efficacy of nortriptyline-fluphenazine with carbamazepine. The sample used 16 patients. VAS measured pain outcome. | Both drugs showed pain relief and did not differ significantly. |

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| No | Author | Title                                                                                                                                                                                                                                                                                                                                 | Methods                                                                                                                                                                                                                                                                                                                                 | Result-Conclusion                                                                                                                                                                                                                      |
|----|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3  | (Jia et al., 2006). | Effects of venlafaxine and carbamazepine for painful peripheral diabetic neuropathy: a randomised, double-blind and double-dummy, controlled multi-centre multi-centre trial                                                                                                                               | The samples involved were 132 diabetic neuropathic pain patients (venlafaxine n = 66, carbamazepine n = 66) from 3 clinics in Chengdu, Chongqing, and Kunming in China. The venlafaxine dose was 25 mg twice a day, while the carbamazepine dose was 100 mg daily; both were given for two weeks. The pain was measured by the Numeric Pain Intensity Scale (NPIS) on days 2, 5, 7, 10, and 14. Quality of life, which included daily activities, work, sleep quality, and mood, was evaluated with a Likert scale (0 = no interference; 10 = unable to sleep) on the days 7 and 14. | The results of this study found that both drugs can reduce pain and improve quality of life, although venlafaxine is more effective than carbamazepine.                                                                                                                                                 |
| 4  | (Maheshwary et al., 2014). | Efficacy and tolerability of carbamazepine for the treatment of painful diabetic neuropathy in adults: a 12-week, open-label, multi-centre multi-centre study                                                                                                          | An efficacy study of carbamazepine was done in 452 patients with diabetic neuropathic pain for 12 weeks, open-label, multi-centre multi-centre (Karachi, Lahore, Islamabad, Peshawar, and Rawalpindi). Carbamazepine at a dose of 400-800 mg/day was given for two days. The dose was titrated from 100 mg on the first day to 400 mg at the end of the first week. The dose was increased to 600-800mg/day, depending on the patient’s response. The measuring instruments used were BPI-sf and the American Chronic Pain Association QoL scale. | After 12 weeks, 73% of patients experienced a reduction in pain >50%, 7% of patients experienced a 100% reduction in pain, and 0.7% did not reduce pain. The quality of life of patients also increased. Side effects that appeared included drowsiness, headache, dizziness, and nausea with an incidence of <1% |
and neuroprotection (Ayano, 2016; Maan et al., 2020). Several studies on the efficacy and safety of carbamazepine in bipolar disorder have been carried out showing that carbamazepine is well-tolerated by bipolar patients at doses of 400-2000 mg/day, and is safe to use in the long term. However, further studies are still needed (Stefano et al., 2018).

The off-label use of carbamazepine

In this study, the off-label use of carbamazepine was found most often in stroke patients. It is estimated that carbamazepine, besides used to treat post-stroke seizures, is also intended for central post-stroke neuropathic pain. Leijon and Boivie examined the use of carbamazepine in central post-stroke pain. In that study, 5 out of 14 patients experienced a decrease in pain, but this was not statistically significant (Leijon and Boivie, 1989). Another use of carbamazepine is for diabetic neuropathic pain and HNP, while in nociceptive pain, carbamazepine use is used in cephalgia. Diagnosis of the nervous system was also mentioned in the medical record, but there was no further explanation regarding the specific disease of the nervous system. The mechanism of carbamazepine for neuropathic pain is the result of blocking Na⁺ channels, which can reduce the excitability of nerve cells. Both central and peripheral neuropathic pain have hyperexcitability characteristics in damaged nerve cells (Jensen, 2002; Wiffen et al., 2013). Several studies of carbamazepine use in D.M. neuropathic pain have been carried out from 1969 to the latest in 2014. The results of these studies included positive responses, reduced pain and improved patient quality of life (Maheshwary et al., 2014; Rull et al., 1969; Wilton, 1974).

In carbamazepine nociceptive pain, it can interfere in GABA-ergic and somatostatinergic signalling (Basbaum et al., 2009; Post, 1988). Research into the use of carbamazepine in nociceptive pain has not been performed yet. Evidence-based on off-label carbamazepine use was found for stroke and D.M. neuropathic pain (13 patients), as shown in Table 3.

Limitations

This research was a retrospective study; data were based on what was written in the medical record. However, this study is expected to provide needed information and may inspire further research.

CONCLUSION

The use of carbamazepine at PKU Muhammadiyah Yogyakarta hospital included 494 prescriptions given to 117 patients. The use was under the distribution permit, with some off-label use. The off-label use of carbamazepine with strong evidence was 24.53%, while other uses were not supported by scientific evidence.

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Conflict of Interest

The authors reported no conflict of interest for this study.

REFERENCES

Ayano, G. 2016. Bipolar Disorders and Carbamazepine: Pharmacokinetics, Pharmacodynamics, Therapeutic Effects and Indications of Carbamazepine: Review of Articles. Journal of Neuropsychopharmacology & Mental Health, 1(4):1–5.

Backonja, M.-M. 2000. Anticonvulsants (Antineuropathics) for Neuropathic Pain Syndromes. The Clinical Journal of Pain, 16(Supplement):S67–S72.

Basbaum, A. I., Bautista, D. M., Scherrer, G., Julius, D. 2009. Cellular and Molecular Mechanisms of Pain. Cell, 139(2):267–284.

Cruccu, G., Gronseth, G., Alksne, J., Argoff, C., Brainin, M., Burchiel, K., Nurmikko, T., Zakrzewska, J. M. 2008. AAN-EFNS guidelines on trigeminal neuralgia management. European Journal of Neurology, 15(10):1013–1028.

Gómez-Pérez, F. J., Choza, R., Ríos, J. M., Reza, A., Huerta, E., Aguilar, C. A., Rull, J. A. 1996. Nortriptyline-fluphenazine vs carbamazepine in the symptomatic treatment of diabetic neuropathy. Arch. Med. Res, 27(4):525–529.

Gupta, S. K., Gupta, A., Mahajan, A., Gupta, R., Tandon, V. R., Gupta, N. 2005. Clinical insights in trigeminal neuralgia. J.K. Science, 7(3):181–184.

Jensen, T. S. 2002. Anticonvulsants in neuropathic pain: rationale and clinical evidence. European Journal of Pain, 6:61–68.

Jia, H., Li, Q., Song, D., An, Z., Liu, Y., Ren, X., Wu, R., Tian, H. 2006. Effects of Venlafaxine and Carbamazepine for Painful Peripheral Diabetic Neuropathy: A Randomized, Double-blind and Double-dummy, Controlled Multi-center. Trial. Chinese
Journal of Evidence-Based Medicine, 6(5):321–328.
Leijon, G., Boivie, J. 1989. Central post-stroke pain — a controlled trial of amitriptyline and carbamazepine. Pain, 36(1):27–36.
Maan, J. S., Duong, H., Saadabadi, A. 2020. Carbamazepine. In StatPearls Publishing, Treasure Island (F.L.).
Maheshwary, N., Saeed, T., Nasrullah, M., Ghafoor, A., Shahid, R., Islam, N., Khattak, M. U., Siddiqi, A., Khan, M. A. 2014. Efficacy and tolerability of carbamazepine for the treatment of painful diabetic neuropathy in adults: a 12-week, open-label, multicenter study. International Journal of General Medicine, 7:339–339.
McQuay, H., Carroll, D., Jadad, A. R., Wiffen, P., Moore, A. 1995. Anticonvulsant drugs for management of pain: a systematic review. BMJ, 311(7012):1047–1052.
National Institute for Health and Care Excellence 2013. Epilepsies: diagnosis and management | Guidance and guidelines.
Post, R. M. 1988. Time course of clinical effects of carbamazepine: implications for mechanisms of action. J Clin Psychiatry, 49:35–48.
Rull, J. A., Quibrera, R., Gonzalez-Millan, H., Castaeda, O. L. 1969. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): Double blind crossover trial. Diabetologia, 5(4):215–218.
Sidhu, H. S., Sadhotra, A. 2016. Current Status of the New Antiepileptic Drugs in Chronic Pain. Frontiers in Pharmacology, 7.
Stefano, G. D., Truini, A., Cruccu, G. 2018. Current and Innovative Pharmacological Options to Treat Typical and Atypical Trigeminal Neuralgia. Drugs, 78(14):1433–1442.
Vargas-Espinosa, M., Sanmarti-Garcia, G., Vazquez-Delgado, E., Gay-Escoda, C. 2012. Antiepileptic drugs for the treatment of neuropathic pain: A systematic review. Medicina Oral Patología Oral y Cirugia Bucal, 17(5):e786–e793.
Wiffen, P. J., Derry, S., Moore, R. A., Aldington, D., Cole, P., Rice, A. S. C., Lunn, M. P., Hamunen, K., Haanpaa, M., Kalso, E. A. 2013. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. In The Cochrane Collaboration (Ed.), Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd, UK.
Wiffen, P. J., Derry, S., Moore, R. A., Mcquay, H. J. 2011. Carbamazepine for acute and chronic pain in adults. In The Cochrane Collaboration (Ed.), Cochrane Database of Systematic Reviews. John