THE OFF-LABEL USE OF OXCARBAZEPINE IN INDONESIA

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\textbf{ABSTRACT}

Oxcarbazepine is a second-generation anticonvulsant drug that is a keto analog of carbamazepine. Oxcarbazepine was approved by The National Agency of Drug and Food Control Indonesia (NA-DFC) for generalized epilepsy, tonic-clonic primary and partial epilepsy with or without secondary generalization. However, as other anticonvulsants, oxcarbazepine is also often used without approved indication (off-label). The aim of this study was to investigate the off-label use of oxcarbazepine through an observational study with retrospective data collection. Data were obtained from four hospitals in Yogyakarta, namely Dr. Sardjito Hospital, UGM Hospital, PKU Muhammadiyah Hospital and Bethesda Hospital. Off-label use of oxcarbazepine was identified based on official registration by NA-DFC Indonesia. The results of this study showed that the use of oxcarbazepine in 2014 was 224 prescriptions, which 117 (52.68\%) was off-label. Most off-label indications according to ICD-10 were cephalgia 48 (41.03\%), followed by trigeminal neuralgia 35 (29.91\%), stroke 6 (5.13\%) and others 29 (23.93\%). From these study, the off-label use of oxcarbazepine was mostly in the cases of neuropathic pain.

\textbf{Keywords}: oxcarbazepine, off-label, indications, Indonesia

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\textbf{PENGGUNAAN OFF-LABEL OKSKARBAZEPIN DI INDONESIA}

\textbf{ABSTRAK}


\textbf{Kata kunci}: okskarbazepin, off-label, indikasi, Indonesia
Introduction

Off-label prescribing refers to understanding the usage of drugs that is officially registered with the indications, dosage, patient age, and route of administration that is different from the description is written on the product information (Gazarian 2007, Le Jeunne et al. 2013, Wittich et al. 2012). The off-label drug usage is prevalent in almost all the world. A study in Germany from 2003-2006 found that off-label drugs usage was 40.2% (Knopf et al. 2013). 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 (Campbell et al. 2003). Drug was found in 86% of prescriptions (at least one off-label drug use) (Ferreira et al. 2012).

A class of drugs often prescribed off-label were 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%) (Stafford 2008). One of the off-label use of anticonvulsants is for neuropathic pain therapy. Carbamazepine is an anticonvulsant that was first investigated for neuropathic pain, especially trigeminal neuralgia (Backonja 2000). Almost all anticonvulsants have pain killer effect in some types of neuropathic pain (Vargas-Espinosa et al. 2012, Wiffen et al. 2013). 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 (Mendlik and Uritsky 2015).

Oxcarbazepine (10,11-dihydro-10-oxo-5H, dibenzo (b, f) azepine-5-carboxamide) is a second-generation anticonvulsant that is a keto analog of carbamazepine. As an analog of carbamazepine, which has been permitted by the FDA as the first line treatment of trigeminal neuralgia, oxcarbazepine has a sodium channel blocking mechanism, thereby reducing hyperexcitability in damaged peripheral nerves. This mechanism is expected to reduce neuropathic pain. Research on animals has shown that oxcarbazepine was effective for neuropathic pain associated with hyperalgesia and allodynia (Jang et al. 2005). Several reviews discussed studies on the analgesic effect of oxcarbazepine in some neuropathic pain such as trigeminal neuralgia, painful diabetic neuroopathy, radiculopathy, and allodynia (Carrazana and Mikoshiba 2003, Zhou et al. 2013).

In 2014, oxcarbazepine was approved by Indonesian NA-DFC for generalized epilepsy, tonic-clonic primary and partial epilepsy with or without secondary generalization. There has been no new indication of the license issued by Indonesian Na-DFC. Data of oxcarbazepine usage in the treatment of neuropathic pain has not been established yet. This study was conducted to determine the off-label use of oxcarbazepine in Yogyakarta, Indonesia. This report is part of the off-label use of anticonvulsant in Indonesia.

Methods

This study was an observational study with retrospective data collection. Data were obtained from the prescription of oxcarbazepine in 2014 derived from four hospitals in Yogyakarta, namely Dr. Sardjito Hospital, UGM Hospital, PKU Muhammadiyah Hospital, and Bethesda Hospital. Indications of oxcarbazepine use were obtained from medical records of patients who receive an oxcarbazepine prescription. The medical record that can not be traced were excluded. The population in this study were all patients who receive an oxcarbazepine prescription in 2014.

Off-label use of oxcarbazepine was determined by evaluating the diagnoses listed in medical records on prescribing oxcarbazepine. This data was then compared to an approved indication by Indonesian NA-DFC in 2014, which was taken from www.pionas.pom.go.id.

Result and Discussion

There were 224 oxcarbazepine prescriptions during the study from four hospitals and 117
(52.23%) was off-label used. The off-label use of oxcarbazepine is summarized in Table 1. There were 18 diagnoses that use off-label of oxcarbazepine. The highest off-label use was cephalgia (41.03%), the second was trigeminal neuralgia (29.91%), and followed by cerebrovascular disease (5.13%). The indications are indicative of a diagnosis that is written in the medical record. The diagnosis was written to the ICD-10 system because Indonesia implements the health insurance system with Indonesia Case Base Groups (INA-CBGs) applications since 2014. INA-CBGs was an application used to file insurance claims to the government. (Permenkes no 27/2014, n.d.; World Health Organization, n.d.). From these data, the uses of oxcarbazepine outside the indications approved by NA-DFC mostly to the cases of neuropathic pain.

**Oxcarbazepine on Neuropathic Pain**

Table 1 showed that the off-label use of oxcarbazepine occurred in the case of neuropathic pain (94.88%) from 117 prescription. Oxcarbazepine expected to have the effect of analgesia for neuropathic pain with a mechanism like carbamazepine by blocking sodium channels that can reduce the excitability of nerve cells. In neuropathic pain, both peripheral and central has the characteristics of their hyperexcitability of the nerve cells if these nerve cells were damaged. The damage to nerve cells that caused a variety of reasons can cause hyperexcitability. In peripheral neuropathic pain, the nerve endings are damaged causing spontaneous pain and increasing 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 by the 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 Gamma Aminobutyric (GABA)-ergic, and changes in calcium influx into the cell. This mechanism has some similarities with the mechanisms involved in epilepsy, and thus many anticonvulsants can be used as an anti-neuropathic pain (Carrazana and Mikoshiba 2003, Jensen 2002, Wiffen et al. 2013, Zhou et al. 2013).

Several studies have been conducted regarding the usage of oxcarbazepine in the treatment of various types of neuropathic pain. Preliminary research in mice found that oxcarbazepine can be utilized for neuropathic pain associated with allodynia or hyperalgesia (Jang et al. 2005). Some reports said that oxcarbazepine was effective and well tolerated for neuropathic pain. Oxcarbazepine efficacy reported in a variety of neuropathic pain, including trigeminal neuralgia, painful diabetic, and patients who are resistant to other anticonvulsants such as gabapentin and carbamazepine. A meta analysis conducted by Carrazana and Mikoshiba found that oxcarbazepine was as efficacious as carbamazepine in reducing pain attack and evoked pain in trigeminal neuralgia (Carrazana and Mikoshiba 2003). Based on preliminary data, oxcarbazepine, topiramate, zonisamide and levetiracetam can be used for various forms of neuropathic pain although without randomized controlled trial studies. Oxcarbazepine, topiramate and zonisamide have unique side effects such as hyponatremia, nephrolithiasis, acute myopia with secondary angle-closure glaucoma; otherwise levetiracetam has lower side effect and also easier to use (no dose adjustment needed in organ dysfunction and no laboratory monitoring required). All 4 agents can be used in the treatment of neuropathic pain in the elderly, especially when carbamazepine, gabapentin or lamotrigine can not be used (Guay 2003). The results from seven open-label clinical study with the same protocol, with different conditions of neuropathic pain, reported that oxcarbazepine was effective as well as safe as a monotherapy in neuropathic pain (Magenta et al. 2005).

The most oxcarbazepine study for neuropathic pain was done on painful diabetic neuropathy. In a multicenter, randomized placebo-controlled study mention that oxcarbazepine clinically reduced diabetic neuropathic pain significantly. Other studies suggest that the use of long-term oxcarbazepine was safe and effective. Although not statistically significant, patients treated oxcarbazepine 1800mg/day showed an improvement in score visual analog scale (VAS) compared to placebo. Oxcarbazepine clinically can reduce the pain of diabetic neuropathy (Beydoun...
et al. 2006, Dogra et al. 2005, Erdemoglu and Varlibas 2006). A review of several double-blind placebo-controlled study of the oxcarbazepine in the treatment of painful diabetic neuropathy and trigeminal neuralgia mention that the use of oxcarbazepine in the treatment of trigeminal neuralgia have strong evidence, while the evidence for treatment diabetic neuropathic pain has not been clear, but a dose of 1800mg/day was well tolerated (Nasreddine and Beydoun 2007).

The use of oxcarbazepine in trigeminal neuralgia has been evaluated in this study. A prospective open-label study of 35 patients with trigeminal neuralgia showed that oxcarbazepine effective from the first month of therapy, decrease pain significantly, and well tolerated. thus, oxcarbazepine is an alternative treatment for trigeminal neuralgia (Gomez-Arguelles et al. 2008). Besi et al. compared the side effects of carbamazepine and oxcarbazepine in the treatment of trigeminal neuralgia and some experienced neurological headache. This observational clinical study concluded that carbamazepine and oxcarbazepine were associated with cognitive impairment. Differences in pharmacokinetics and pharmacodynamics profile is an explanation of differences in adverse effects both on a different gender. Women are more susceptible to the adverse effects at low doses. The side effects of anticonvulsant drugs are the main reason for replacement therapy or recommendation for surgery in trigeminal neuralgia (Besi et al. 2015).

Other studies on the use of oxcarbazepine in another neuropathic pain were done in a migraine, complex regional pain syndrome type 1, and tremor. Oxcarbazepine was effective and safe for treatment a neuropathic pain. Oxcarbazepine is also an alternative therapy if the patient has neuropathic pain resistant to gabapentin (Lalwani et al. 2005, Raj et al. 2006, Silberstein et al. 2008).

A randomised, double-blind, placebo-controlled, phenotype-stratified study, with oxcarbazepine therapy (1800-2400mg) and placebo for 2-6 weeks treatment periods, obtained that oxcarbazepine more effectively reduces peripheral neuropathic pain in patients with irritable nociceptors phenotype compared with a non-irritable phenotype (Demant et al. 2014).

A systematic review of randomized controlled trial studies and cross-over studies conducted by Zhou et al. (2013) obtain evidence with the medium quality for use oxcarbazepine in diabetic neuropathic pain. The meta-analysis did not included the negative outcomes of the test. There is no evidence of efficacy for other neuropathic pain, except low-quality evidence on radiculopathy. Side effects that arise are weak to moderate, adverse events leading to discontinuation of the drug does not exist. A randomized-controlled study on the efficacy oxcarbazepine on various types of neuropathic pain is still required (Zhou et al. 2013).

In central neuropathic pain, the research found only one open-label pilot study in 12 patients with multiple sclerosis (MS) in the case of painful paroxysmal symptoms (PPS) where oxcarbazepine well tolerated in most patients. Possible use for pain in MS, but the efficacy of the PPS still to be clarified with larger studies (Solaro et al. 2007). Generally, oxcarbazepine can be used for neuropathic pain associated with allodynia and hyperalgesia, although research is not sufficient. There is an indication that is also not clear about prescribing oxcarbazepine, which is indicative of drug eruption. In medical records no history of other anticonvulsants, so it can not be recognized the purposes of oxcarbazepine administration, as a replacement therapy or as an anti-pain to pain arising from drug eruption. Thus the findings of the use of oxcarbazepine in neuropathic pain in this study some have strong evidence.
Table 1. The Off-Label Use of Oxcarbazepine in 2014 From Four Hospitals in Yogyakarta, Indonesia

<table>
<thead>
<tr>
<th>No.</th>
<th>Indication</th>
<th>ICD10 Code</th>
<th>Diagnosis</th>
<th>Amount</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Neuropathic Pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Cephalgia</td>
<td>R51</td>
<td>48</td>
<td>48</td>
<td>41.03</td>
</tr>
<tr>
<td>2</td>
<td>Trigeminal neuralgia</td>
<td>G50.0</td>
<td>35</td>
<td>35</td>
<td>29.91</td>
</tr>
<tr>
<td>3</td>
<td>Cerebrovascular disease</td>
<td>I60-I69</td>
<td>6</td>
<td>6</td>
<td>5.13</td>
</tr>
<tr>
<td>4</td>
<td>Dorsalgia</td>
<td>M54</td>
<td>4</td>
<td>4</td>
<td>3.42</td>
</tr>
<tr>
<td>5</td>
<td>Personal history of disease of the nervous system</td>
<td>G00-G99</td>
<td>4</td>
<td>4</td>
<td>3.42</td>
</tr>
<tr>
<td>6</td>
<td>Vertigo</td>
<td>R42</td>
<td>2</td>
<td>2</td>
<td>1.71</td>
</tr>
<tr>
<td>7</td>
<td>Other postsurgical states</td>
<td>Z98</td>
<td>2</td>
<td>2</td>
<td>1.71</td>
</tr>
<tr>
<td>8</td>
<td>Herpes zoster</td>
<td>B02</td>
<td>2</td>
<td>2</td>
<td>1.71</td>
</tr>
<tr>
<td>9</td>
<td>Jaw joint disorders</td>
<td>K05.3</td>
<td>2</td>
<td>2</td>
<td>1.71</td>
</tr>
<tr>
<td>10</td>
<td>Myalgia</td>
<td>M79.1</td>
<td>1</td>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td>11</td>
<td>Injuries of head</td>
<td>S09</td>
<td>1</td>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td>12</td>
<td>Benign neoplasms: meninges</td>
<td>D32.9</td>
<td>1</td>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td>13</td>
<td>Adhesive capsulitis of shoulder</td>
<td>M75</td>
<td>1</td>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td>14</td>
<td>Cervicobrahnic syndrome</td>
<td>M53.1</td>
<td>1</td>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td>15</td>
<td>Drug eruption</td>
<td>L27</td>
<td>1</td>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>111</td>
<td>94.88</td>
</tr>
<tr>
<td></td>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Dengue Haemorrhagic Fever</td>
<td>A97</td>
<td>3</td>
<td>3</td>
<td>2.56</td>
</tr>
<tr>
<td>2</td>
<td>Cytomegalovirus</td>
<td>B25</td>
<td>2</td>
<td>2</td>
<td>1.71</td>
</tr>
<tr>
<td>3</td>
<td>Acute gastroenteritis</td>
<td>A08</td>
<td>1</td>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>6</td>
<td>5.12</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>117</td>
<td>100</td>
</tr>
</tbody>
</table>

**Oxcarbazepine on infection**

The use of oxcarbazepine in infectious diseases is not associated with neuropathic pain, found in DHF infection, CMV, and the GEA. In the medical record no other diagnosis that is written on the prescription oxcarbazepine. This use is not clear yet to address specific symptoms or diagnosis because the data are retrospective data. It is estimated that the provision oxcarbazepine, in this case, related to the possibility of high fever in DHF and CMV that can cause seizures. This ambiguity is the ambiguity indication oxcarbazepine, in this case, is included the use of off-label or not. While the GEA-related cramps that often occurs in patients with GEA, so oxcarbazepine expected to relieve cramps through the mechanism of inhibition of the sodium channel. No evidence found in this case.

**Conclusion**

In Yogyakarta in 2014, there were 224 prescriptions of oxcarbazepine, of which 117 (52.23%) were prescribed off-label. Most off-label indications according to ICD-10 were cephalgia 48 (41.03%), followed by trigeminal neuralgia 35 (29.91%), stroke 6 (5.13%) and others 29 (23.93%).

**Acknowledgment**

References


