Evaluation of hematologic profile may be needed for patients treated with oxcarbazepine

Running Title: Oxcarbazepine induced leukopenia

Gu Hyun Jung, MD, Su Jeong You, MD, PhD

Department of Pediatrics, Inje University Sanggye Paik Hospital, Seoul, Korea

Corresponding author:

Su Jeong You, MD, PhD

Department of Pediatrics, Inje University Sanggye Paik Hospital

1342 Dongil-ro, Nowon-gu, Seoul 01757, Korea

Tel: +82-2-950-1080

Fax: +82-2-951-1246

E-mail: su6236@naver.com
Abstract

**Purpose:** The major side effects of treatment with oxcarbazepine (OXC) are skin rash and hyponatremia. Hematologic side effects are reported to be rare. The aim of this study was to investigate the rate and types of hematologic side effects of OXC.

**Methods:** The medical records of 184 patients who were diagnosed with epilepsy or movement disorder and treated with OXC monotherapy at the Department of Pediatrics of Sanggye Paik Hospital from July 2001 to July 2018 were retrospectively reviewed.

**Results:** Of the 184 patients, 10 (5.4%) developed leukopenia including pancytopenia and two (1.0%) developed pancytopenia. Leukopenia occurred 11 days to 14 years after OXC administration and was more frequent in males than in females (9 vs. 1, \( P < 0.05 \), Fisher’s exact test). Of the eight patients with leukopenia alone, seven continued OXC treatment; six improved without intervention; one was lost to follow-up; and one, who received a reduced OXC dose, improved after intervention. Pancytopenia occurred within 2 months from initiation of OXC treatment. Both patients initially continued OXC. One improved within 1 month and continued OXC, but the other showed progression, leading to a discontinuation of OXC and improvement within 1 month. There were no statistically significant differences in patient age, OXC dose, and duration of OXC treatment between patients with and without these side effects of OXC (\( P > 0.05 \), t-test).

**Conclusion:** OXC-induced leukopenia is not rare and may result in pancytopenia. Patients being treated with OXC should be regularly monitored for abnormal CBC profiles.

**Keywords:** Oxcarbazepine, Complete blood count, Leukopenia, Pancytopenia
Key message

Question: Will oxcarbazepine cause hematologic side effects to the patients?

Finding: We found that oxcarbazepine can lead to leukopenia and pancytopenia. Oxcarbazepine-induced leukopenia is not rare (5.4%) and can lead to pancytopenia (1.0%). Both of them were occurred by chance without any symptom.

Meaning: Oxcarbazepine can induce leukopenia and pancytopenia, so evaluation of hematologic profile may be needed during oxcarbazepine therapy.
Introduction

Patients with pediatric epilepsy and movement disorders require long-term treatment with anticonvulsants. Drug selection is important in minimizing side effects. Oxcarbazepine (OXC), a keto derivative of carbamazepine (CBZ), is widely used as an alternative to CBZ for the treatment of children with partial, secondary generalized epilepsy and movement disorders.\(^1\) Compared with CBZ, OXC has similar efficacy in reducing seizures but fewer side effects.\(^2,3\) The most common side effects of OXC are skin rash, headache, dizziness, nausea, sedation and hyponatremia.\(^4\) However, in contrast to CBZ, which has been associated with blood dyscrasias,\(^5\) OXC is relatively safe hematologically.\(^6,7\) Although a few case reports have described leukopenia associated with OXC, all of these patients were receiving other agents in addition to OXC, such as levetiracetam and clonazepam\(^8\) or valproic acid.\(^9\) Another case report described pancytopenia associated with OXC in an adult, but this patient was taking sertraline, fosinopril, clonazepam and an oral contraceptive, in addition to OXC.\(^10\) Of 42 children being treated with OXC monotherapy, one (2.3%) developed leukopenia, leading to the withdrawal of OXC.\(^11\) However, to our knowledge, there have been no reports of OXC-associated pancytopenia and no studies on hematologic dysfunction in patients being treated with this agent. This retrospective, single center study assessed the rates of OXC-associated leukopenia and pancytopenia in pediatric patients.
Materials and Method

2.1 Patients

Patients aged < 18 years who were diagnosed with epilepsy or a movement disorder and treated with OXC from July 2001 to July 2018 at Sanggye Paik Hospital were evaluated retrospectively. Patients were excluded if they also had other conditions that could lead to abnormalities in hematopoietic function, such as infectious diseases, trauma, and surgery. Of the 420 patients treated with OXC during this time period, 236 were excluded, 215 patients because they received polytherapy and 21 because their complete blood counts (CBC) were not determined. Finally, 184 patients were included. Data collected from all patients included age at OXC administration, gender, diagnosis, duration of OXC treatment, maintenance OXC dose, hemoglobin concentration, white blood cell (WBC) count, platelet count, and absolute neutrophil count (ANC). The onset and improvement of leukopenia were determined.

Patients were divided into two groups: those with and those without OXC-associated leukopenia, which was defined as a WBC count < 4.0 x 10³/µL. Among the patients with leukopenia, those with pancytopenia, defined as anemia, thrombocytopenia, as well as leukopenia, were described in detail.

The study protocol was approved by the institutional review board of Sanggye Paik Hospital. (2018-10-016)

2.2 Statistical analyzes

Continuous variables, including age, duration of treatment, maintenance dose of OXC and CBC profile, were expressed as mean ± standard deviation (SD) and compared using t-tests. Categorical variables were compared using chi-squared test. All statistical analyses were
performed using IBM SPSS statistics 25.0 software, with statistical significance defined as a $P$-value $< 0.05$. 
Results

During the study period, 184 children, 104 boys and 80 girls, were treated with OXC. Of these, 174 (94.8%), 95 boys and 79 girls, did not develop leukopenia. Their mean age at OXC administration was 8.02 ± 3.41 years, their mean duration of OXC treatment was 40.03 ± 37.80 months, and their mean maintenance dose of OXC was 15.27 ± 7.40 mg/kg/day. Leukopenia was observed in 10 (5.2%) children, nine boys and one girl. The mean age at OXC administration was 8.00 ± 3.36 years, their mean duration of OXC treatment was 71.80 ± 57.84 months, and their mean maintenance dose of OXC was 15.2 ± 7.08 mg/kg/day. The percentage of boys was significantly higher in the leukopenia group (P < 0.05, Fisher’s exact test), whereas age at OXC administration, duration of OXC treatment, and dose of OXC did not differ significantly in the two groups (Table 1).

Leukopenia was first observed 11 days to 14 years after OXC administration (Fig.1). Eight patients who had leukopenia alone showed a decrease in average leukocyte count from 6111/µL (range, 4850–7700/µL) to 3710/µL (range, 3110–3950/µL) and in ANC from 3552.5/µL (range, 2490–4930/µL) to 1602.5/µL (range, 850–2340/µL). After developing leukopenia, seven patients continued taking OXC, with six improving without further intervention, and one patient lost to follow-up. In one patient, who experienced reductions in leukocyte count to 3110/µL and in ANC to 850/µL, OXC dose was reduced from 8.8 mg/kg to 6.6 mg/kg, increasing the leukocyte count to 5990/µL and ANC to 3380/µL. This patient was continued on the reduced OXC dose.

Of the 184 patients, two patients (1.0%) developed pancytopenia (Table 2). One patient, a boy aged 3 years 6 months diagnosed with focal epilepsy, was started on 5 mg/kg/day OXC monotherapy during the first week, with the dose increased to 11 mg/kg/day during the second week. After 28 days, his CBC profile was hemoglobin concentration 11.6 g/dL,
leukocyte count 2690/µL, platelet count 129,000/µL, and ANC 500/µL. He continued to take OXC, normalizing after another 28 days, as shown by hemoglobin concentration 12.3 g/dL, leukocyte count 7330/µL, platelet count 251,000/µL and ANC 3230/µL. He was maintained on OXC for 2 years with no recurrence of pancytopenia. The second patient with pancytopenia was a girl aged 9 years 5 months diagnosed with benign childhood epilepsy with centrotemporal spikes. Before OXC administration, her CBC profile was hemoglobin concentration 13.8 g/dL, leukocyte count 7190/µL, platelet count 186,000/µL, and ANC 2910/µL. She developed leukopenia after 26 days of OXC treatment, as shown by a leukocyte count of 3510/µL and an ANC of 1520/µL. She continued taking OXC without intervention. A follow-up CBC after 53 days of treatment with 20 mg/kg/day OXC resulted in the development of pancytopenia, with a hemoglobin concentration of 10.0 g/dL, a leukocyte count of 2620/µL, a platelet count of 102,000/µL, and an ANC of 1310/µL. OXC was discontinued, resulting in CBC normalization, as shown by hemoglobin concentration 14.1 g/dL, leukocyte count 4340/µL, platelet count 188,000/L, and ANC 2290/µL. Subsequently, she was started on levetiracetam. Neither of these patients developed symptoms during periods of pancytopenia.
Discussion

OXC, the 10-keto analogue of CBZ, is metabolized to 10,11-dihydro-10-hydroxy carbamazepine (mono-hydroxy derivative, MHD), which has antiepileptic effects.\(^\text{12}\) MHD binds to sodium channels, inhibiting sodium uptake and subsequent high-frequency repetitive firing.\(^\text{13}\) Hyponatremia is the most common side effect in patients treated with OXC, with other side effects including skin rash, headache, dizziness, and nausea.\(^\text{4}\)

The hematologic side effects of AEDs, including leukopenia, thrombocytopenia, anemia, and aplastic anemia can lead to serious, life-threatening events. Several hypotheses have been proposed to explain the mechanisms by which a drug causes hematologic side effects, including bone marrow suppression, destruction of immune system related cells, and direct marrow toxicity.\(^\text{14, 15}\) Neutropenia or agranulocytosis is more common than the other drug-associated blood dyscrasias.\(^\text{16}\) Mild leukopenia is relatively common,\(^\text{17}\) whereas aplastic anemia and pancytopenia are rare.\(^\text{18}\) Other AEDs are better known for their hematologic side effects. For example, long term phenytoin can cause mild leukopenia; valproic acid can cause thrombocytopenia and inhibit platelet aggregation;\(^\text{17}\) and felbamate can cause aplastic anemia, limiting its use.\(^\text{19, 20}\)

Although OXC has been reported to be relatively safe hematologically, this study showed that OXC can have an effect on the hematopoietic system. Its mechanism of action is unknown, but it is likely to be related with bone-marrow toxicity similar to that of CBZ because of their structural similarity.\(^\text{5}\) CBZ can induce leukopenia and aplastic anemia,\(^\text{21}\) with blood dyscrasias induced by toxic metabolites,\(^\text{5}\) suggesting similar mechanisms for the hematologic side effects of OXC.

This study reported the incidence, characteristics and outcomes of OXC-induced leukopenia and pancytopenia. Leukopenia in these patients was likely due to OXC because
we excluded patients with other inducers of leukopenia such as other drugs, infection, trauma, and surgery. The incidence of leukopenia was not rare (5.2%), although our finding, that most of these patients were asymptomatic, suggested that the incidence of leukopenia may be higher. Two patients (1.0%) showed progression to pancytopenia, further indicating that OXC can affect the hematopoietic system and may cause serious side effects.

Except for male over-predominance in the leukopenia group, patient characteristics did not differ significantly in the groups with and without leukopenia. Six (60%) patients developed hematologic side effects within 2 months (range, 11-53 days) after starting OXC, whereas the other four (40%) took OXC for more than 3 years (range, 3–14 years). However, there was no significant difference between early and late onset OXC induced leukopenia, suggesting that it occurred by chance during maintenance treatment. Because side effects can occur at any time during treatment, CBC should be monitored continuously during treatment with OXC.

Most patients recovered spontaneously from leukopenia despite continuing the medication. However, a few patients developed serious side effects of pancytopenia, necessitating drug withdrawal or dose reduction. One patient maintained on OXC showed progression to pancytopenia, which improved after discontinuation of OXC. Continuation of OXC may worsen a patient’s condition, making early detection important.

This study had several limitations, including its retrospective, single center design. Moreover, CBC was not routinely performed long-term in all patients. This may result in an inaccurate assessment of incidence, which may have been underestimated. In addition, it was difficult to compare patient characteristics due to large differences in the number of patients with and without side effects. Nevertheless, this study is the first to investigate the hematologic side effects of OXC. Further long-term prospective studies are needed.
In conclusion, OXC-induced leukopenia is not rare and may lead to pancytopenia. CBC should be regularly monitored during treatment with OXC, regardless of whether or not patients have abnormal CBC profiles.

Conflict of interest

No potential conflict of interest relevant to this article was reported.
Reference


11. Serdaroglu G, Kurul S, Tutuncuoglu S, Dirik E, Sarioglu B. Oxcarbazepine in the


Table 1. Baseline clinical characteristic of patients treated by oxcarbazepine

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Without adverse effects (n = 174)</th>
<th>With leukopenia or pancytopenia (n = 10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± standard deviation)</td>
<td>8.02 ± 3.41</td>
<td>8.00 ± 3.36</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>95 (54.6%)</td>
<td>9 (90%)</td>
<td>0.028†</td>
</tr>
<tr>
<td>Female</td>
<td>79 (45.4%)</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Duration of oxcarbazepine (months, mean ± standard deviation)</td>
<td>40.03 ± 37.80</td>
<td>71.80 ± 57.84</td>
<td>&gt; 0.05‡</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>168 (96.5%)</td>
<td>9 (90%)</td>
<td>&gt; 0.05‡</td>
</tr>
<tr>
<td>Movement disorder</td>
<td>6 (3.5%)</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Dose of oxcarbazepine (mg/kg, mean ± standard deviation)</td>
<td>15.27 ± 7.40</td>
<td>15.2 ± 7.08</td>
<td>&gt; 0.05‡</td>
</tr>
</tbody>
</table>

† t-test

‡ Fisher’s exact test

‡ Chi-squared test
<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>3y6m</td>
<td>9y5m</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Focal epilepsy</td>
<td>Benign childhood epilepsy with centrottemporal spikes</td>
</tr>
<tr>
<td><strong>Timing of leukopenia</strong></td>
<td>28 days</td>
<td>26 days</td>
</tr>
<tr>
<td><strong>Timing of pancytopenia</strong></td>
<td>28 days</td>
<td>53 days</td>
</tr>
<tr>
<td><strong>Dose of Oxcarbazepine</strong></td>
<td>11mg/kg/day</td>
<td>20mg/kg/day</td>
</tr>
<tr>
<td><strong>CBC finding</strong></td>
<td>(Baseline/onset/improving)</td>
<td>(Baseline/onset/progressing/improving)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>-/11.6/12.3</td>
<td>13.8/13.7/10.0/14.1</td>
</tr>
<tr>
<td>WBC (uL)</td>
<td>-/2690/7330</td>
<td>7190/3510/2620/4340</td>
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<td>Platelet (uL)</td>
<td>-/129k/251k</td>
<td>186k/171k/102k/188k</td>
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<tr>
<td>Absolute neutrophil count</td>
<td>-/500/3230</td>
<td>2910/1520/1310/2290</td>
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<tr>
<td>Peripheral blood smear</td>
<td>Not done</td>
<td>Mild neutropenia &amp; thrombocytopenia</td>
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<tr>
<td>Symptoms of pancytopenia</td>
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<td>None</td>
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<tr>
<td>Other adverse effects</td>
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<td>Other abnormal lab finding</td>
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<tr>
<td><strong>Management</strong></td>
<td>Observation</td>
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<tr>
<td><strong>Improving date after pancytopenia</strong></td>
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<tr>
<td><strong>Intervention</strong></td>
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Fig. 1 Onset of leukopenia after oxcarbazepine administration.