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Case Report

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Neutropenia Associated With Topiramate Monotherapy: Adverse Effects Associated With Topiramate Usage

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Abstract

Topiramate is a well-known anti-epileptic drug and used in the migraine prophylaxis. Topiramate has various effects on different receptors and enzymes. Beholding the result, drug has many central nervous system (CNS)-related and systemic adverse effects. It has also hematopoietic adverse effects, but these effects are very rare and associated with previous or concomitant use of sulfonamides which inhibit carbonic anhydrase. A 33-year-old female patient who had migraine without aura diagnosis for nearly 13 years was admitted to outpatient clinic with symptoms of nausea, fatigue and malaise. She had no medication except for eletriptan (40 mg during attack) which was introduced to her 5 months ago and topiramate (100 mg/day) which was introduced 5 weeks ago with a dose of 25 mg/day and escalated to current dose in 4 weeks. Complete blood cell count revealed low white blood cells and low neutrophil. We presented a case which had a clinically important hematologic adverse reaction associated with newly introduced topiramate treatment without any previous or concurrent sulfonamide usage. Topiramate is a sulfa-derivative monosaccharide that is used for treating epilepsy (1996) and migraine (2004), but other indications include infantile spasms, psychiatric disorders, neuropathic pain, weight reduction, tobacco dependence, essential tremor and post-herpetic neuralgia. Topiramate, one of these novel anti-epileptic drugs, is associated with hematologic adverse reactions. According to our knowledge, this report of hematologic adverse effects associated with topiramate without previous or concurrent usage of sulfonamides is first in the literature.

Keywords: Topiramate; Migraine; Leucopenia

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Introduction

Migraine is a common neurological disorder that can significantly impair the quality of life of patients. The prevention of disease-related disability is the ultimate goal of successful migraine treatment. Anti-epileptic drugs which affect sodium channels have a potential in migraine treatment. Topiramate is a well-known anti-epileptic drug and used in the migraine prophylaxis of adults and children with a dose of 100 - 200 mg/day. Topiramate is a sulfa-derivative monosaccharide [1]. Topiramate has various effects on different receptors and enzymes. These interactions can be classified as: increasing gamma-aminobutyric acid (GABA) activity at GABA-A receptors; inhibiting carbonic anhydrase isoenzymes II and IV; blocking voltage-dependent sodium and calcium channels; antagonism of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate subtype of the glutamate receptor and antagonism of 5-HT2C receptors [2]. Although it is not clear, effect mechanism of topiramate on migraine is thought to be associated with decreased cortical excitability along with association of one or more mechanisms mentioned above [3, 4]. Most potential adverse effects of topiramate usage also depend on these interactions. For instance, antagonism of 5-HT2C receptors is found to be associated with anorexia whereas carbonic anhydrase inhibition is associated with metabolic acidosis and paresthesias. The cause of central nervous system (CNS) adverse effects is less clear, and in many cases these adverse effects are dose-related. Known systemic adverse effects of topiramate include weight loss, anorexia, nausea along with other gastrointestinal adverse events, paresthesias, metabolic acidosis and hypokalemia, renal calculi, glaucoma (including angle closure glaucoma), rash and Stevens-Johnson syndrome. Known CNS adverse effects of topiramate are cognitive impairment, fatigue, palinopsia, tremor and myoclonus. Topiramate has also hematopoietic adverse effects, but these effects are very rare and associated with previous or concomitant use of sulfonamides which inhibit carbonic anhydrase [5].

Hereby, we present a case of topiramate-induced leukopenia which occurred during the fifth week of treatment. According to our knowledge, this report is unique regarding occurrence of such complication associated with topiramate monotherapy.

Case Report

A 33-year-old female patient who had migraine without aura

Table 1. Blood Cell Counts of the Patient Acquired at the Admission and Seventh Day, 14th Days and 16th Week After Ceasing Topiramate Medication

	White blood cell (10^3/µL)	Neutrophil (10^3/µL)
Admission	2.2	0.4
Seventh day	3.7	1.1
Fourteenth day	6.1	2.4
Sixteenth week	7.4	3.9

Normal ranges: white blood cells: 4.3 - 10.3 × 10^3/µL, neutrophil: 2.1 - 6.1 × 10^3/µL.

diagnosis for nearly 13 years was admitted to outpatient clinic with symptoms of nausea, fatigue and malaise. Her medical reports revealed that she had a migraine attack frequency of 6 - 8 per month, and her attacks lasted 10 - 14 h on average. She had no medication except for eletriptan (40 mg during attack) which was introduced to her 5 months ago and topiramate (100 mg/day) which was introduced 5 weeks ago with a dose of 25 mg/day and escalated to current dose in 4 weeks. At the beginning of topiramate administration, her MIDAS score was 23. She reported a decrease in attack frequency with topiramate medication.

Physical and neurologic examination revealed no abnormalities. She had a body temperature of 36. 8 °C, blood pressure of 120/85 mm Hg and heart rate of 83 bpm. Laboratory test results were in normal range by means of biochemical tests. Complete blood cell count revealed low white blood cells (2.2 × 10^3/µL, normal range: 4.3 - 10.3 × 10^3/µL), low neutrophil (0.4 × 10^3/µL, normal range: 2.1 - 6.1 × 10^3/µL). Serologic test for hepatitis A, B and C, rubella, HIV, Epstein-Barr virus, parvovirus, toxoplasma and cytomegalovirus were normal. Gruber-Widal test and tests of anti-nuclear antibody and anti-dsDNA were also normal. There were no traces of blast cell on peripheral blood smear. Abdominal ultrasonography was normal which was performed to exclude intra-abdominal organ pathologies. Axillary and neck ultrasonography revealed no signs of lymphadenopathy.

After ceasing the topiramate treatment, blood cell counts were started to recover. Laboratory tests reached normal ranges at the end of the second week (Table 1).

Discussion

We presented a case which had a clinically important hematologic adverse reaction associated with newly introduced topiramate treatment. Patient presented with leukopenia/neutropenia. After investigation of other possible causes and establishing the correct diagnosis, medication of topiramate ceased. Patient's hematologic abnormalities gradually recovered afterwards.

Topiramate is a sulfa-derivative monosaccharide that is used for treating epilepsy (1996) and migraine (2004), but other indications include infantile spasms, psychiatric disorders, neuropathic pain, weight reduction, tobacco dependence, essential tremor and post-herpetic neuralgia [6]. Topiramate blocks voltage-gated sodium channels, hyperpolarizes potassium currents, enhances postsynaptic GABA receptor activity, suppresses the AMPA/kainate receptor, reduces glutamate excitatory activity and inhibits some carbonic anhydrase isoenzymes [2]. In humans and other mammals, sulfonamides (acetazolamide, zonisamide, methazolamide and sulthiame) and sulfamates (topiramate) inhibit carbonic anhydrase and act as anti-epileptic drugs [7]. Association of carbonic anhydrase activity and seizure development is not clear; however, specific subtypes of carbonic anhydrase seem to contribute to the aggravation of seizures in the CNS by signaling GABA-ergic neurons, altering the pH and stimulating excitatory N-methyl-D-aspartate (NMDA) receptors [7]. Discovery of carbonic anhydrase isozymes specifically expressed in the brain stimulated the development of carbonic anhydrase inhibitors as novel anti-epileptic drugs [1]. Topiramate, one of these novel anti-epileptic drugs, is associated with hematologic adverse reactions [8]. Hematologic adverse reactions due to sulfonamide usage are classified into three categories: 1) immuno-allergic reaction to drugs; 2) dose-dependent toxicity of the drugs; and 3) cross-sensitivity between sulfonamides. Severe agranulocytosis associated with sulfonamides and hematologic reactions caused by cross sensitivity between sulfonamides are reported previously [9, 10]. According to our knowledge, this report of hematologic adverse effects associated with topiramate without previous or concurrent usage of sulfonamides is first in the literature.

Conclusion

Sulfa-derivative drugs may cause hematologic adverse effects. Concurrent or previously introduced sulfonamides also cause such adverse effects due to cross-sensitivity. In this report we presented a case with topiramate monotherapy associated with leukopenia without any previous or concurrent sulfonamide usage. Clinician must be aware of serious side effects of topiramate especially at the beginning of the treatment. Leukopenia should be considered along with the other insignificant complaints such as nausea, fatigue and malaise.

Conflict of Interest

No conflicts of interest to declare.

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