Oseltamivir (Tamiflu) Induced Depressive Episode in a Female Adolescent

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Oseltamivir was developed for prophylactic and therapeutic use against influenza, specifically targeting the viral enzyme's highly-conserved active site. In recent years, there have been case reports of neuropsychiatric events during or after oseltamivir treatment, in Japan and other countries. However, a search of the literature revealed no such cases in South Korea. We present the case of a 15-year-old female adolescent diagnosed with depressive episode after taking oseltamivir. Oseltamivir is generally well tolerated. Its most frequent adverse effects include nausea and vomiting, diarrhea, and abdominal pain. In influenza patients taking oseltamivir, neuropsychiatric adverse events include delirium, behavioral disturbance, suicide, delusion, panic attack, convulsion, depressed mood, loss of consciousness, etc. Reportedly, such neuropsychiatric adverse events were more common in children than in adults and generally occurred within 48 hours of administration. Here, we report a retrospective review case of an oseltamivir-related neuropsychiatric event in a female adolescent in South Korea.

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Key Words Oseltamivir, Depressive episode, Adolescent.

INTRODUCTION

Worldwide, seasonal influenza generally arises each year, due to a recombination of the influenza virus.¹ In early April 2009, the medical community identified the pandemic influenza A (H1N1) virus, which spread rapidly through the world. Oseltamivir gained great attention after the onset of the 2009 pandemic due to the influenza A (H1N1) virus.² The drug has significant antiviral, biochemical, and clinical effects in human influenza virus infections. Oseltamivir is a prodrug of oseltamivir carboxylate, a potent and selective inhibitor of neuraminidase. Hepatic esterase metabolizes this prodrug to the active metabolite, oseltamivir carboxylate, which is not metabolized further.³⁻⁵

Oseltamivir was well tolerated, with an adverse effect incidence comparable to that of the placebo recipients in its clinical trials.⁶ The most commonly reported adverse effects, in clin-

ical trials of both healthy young adults and high-risk patients, were gastrointestinal discomforts, including nausea and vomiting. These generally occurred upon treatment initiation and resolved within 2 days. Other adverse effects included diarrhea, abdominal pain, epistaxis, ear disorders, rash, swelling of the face or tongue, toxic epidermal necrolysis, arrhythmia, dizziness, and conjunctivitis.^{5,6} Oseltamivir has no known drug-drug interactions or adverse events from reported overdoses.²

Recently, several reports from Japan showed that some oseltamivir-treated children had experienced adverse neuropsychiatric events.^{2,7,8} More than 100 cases of abnormal behaviors and 70 deaths, involving children and adolescents, occurred in association with oseltamivir use in Japan.⁹ There was a reported case of mania associated with oseltamivir use in a Chinese patient.¹⁰ Another report described delirious behavior in pediatric patients following the use of oseltamivir.¹¹ To estimate the incidence rate of adverse neuropsychiatric events in patients given oseltamivir, Toovey et al.⁷ conducted an analysis covering Japan, the US, and other countries and finding such neuropsychiatric events generally fell into the categories of abnormal behaviors, delusions, and perceptual disturbances. In addition, there were cases of delirium and delirium-like events, depressed consciousness levels, parasomnia, suicidal events, accidents, and injuries. The incidence rate was reportedly higher in male than in female patients. Most such events oc-

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curred within the first 2 days of oseltamivir treatment.⁴

A search of the literature revealed few cases of oseltamivir-induced depressive episodes in South Korea. We present a case involving a 15-year-old girl with depressive neuropsychiatric symptoms after receiving oseltamivir for the treatment of influenza.

CASE

A 15-year-old girl visited our outpatient clinic with symptoms of agitation, euphoric mood, flight of ideas, excessive talking, auditory hallucinations, and decreased need for sleep. She was attending an international school in Thailand and had a very good record at school.

Looking at her premorbid features, she fulfilled her responsibility for school life and was sincere in every work. She underwent normal development. In a Thailand international school, she enjoyed school life and had good relationship with friends. Her favorite activities were reading and drawing. She could easily concentrate on something and performed good academic achievement. She had no family history of mood disorder or psychotic disorder.

She had complained of stuffy nose, sore throat, and high fever symptoms 3 months ago, and she had gone to the hospital for a physical examination. At that time, she received a rapid diagnostic test for influenza A virus infection. The doctor suspected an influenza A virus infection and prescribed oseltamivir for her, as 75 mg of oral oseltamivir, twice daily, for five days. Her symptoms improved one day after beginning the medicine.

On her third day taking oseltamivir, the patient became extremely nervous and had difficulty making decisions. However, she completed the 5-day oseltamivir treatment. On that 5th day, she had no need for sleep. She could not sleep at all. She was depressed, experienced loss of appetite, and found it hard to concentrate on conversation and her schoolwork, such as reading books. She experienced a very intense suicidal ideation, reporting that she thought, "How about falling from a balcony?"

The patient visited a psychiatry clinic and received a 2-month prescription for antidepressants. Subsequently, her mood improved slightly and she could sleep. Her suicidal ideation stopped. Therefore, the clinic reduced her antidepressants. A week before her visit to our clinic, her aspect became very different. She felt herself to be the most special person. She felt very confident, with a greatly elated mood. She was more energetic than usual, sleeping less and talking more. She thought that she understood everything. As the week passed, her symptoms worsened, and she began experiencing auditory hallucinations.

The patient visited our psychiatry clinic with the above symp-

toms, accompanied by her mother. We believed she was in a manic state and prescribed lithium and antipsychotic drugs: 150 mg/day lithium and 100 mg/day quetiapine, to start. We then increased the drug dosage systematically. Her symptoms began to improve within a few days and resolved completely after a month.

DISCUSSION

Oral oseltamivir administration is a known efficacious therapy for influenza in children, when given within 48 hours of the illness's onset. Oseltamivir treatment is generally well tolerated, with a low incidence of adverse effect. The most common adverse effects, nausea and vomiting at the start of treatment, generally are mild to moderate and resolve in 1-2 days. In children taking oseltamivir, emesis of mild or moderate intensity and short duration was more frequently reported.^{1,2,5,6} Reportedly, there were also numerous incidences of delirium, encephalopathy, abnormal behavior, and other neuropsychiatric events after oseltamivir administration.^{8,10-12} It seems oseltamivir might cause mental instability and suicidal tendencies, and it is critical to determine oseltamivir's neuropsychiatric effects and establish methods for its safe administration.^{8,9}

Reportedly, adverse neuropsychiatric events in influenza patients treated with oseltamivir were more common in children and generally occurred within 48 hours of the influenza illness's onset and the initiation of treatment. When Toovey et al.⁷ categorized the reported events per International Classification of Diseases (9th edition) codes, abnormal behavior and delusions/perceptual disturbances were the largest categories, and delirium or delirium-like events were very common within most categories. The abnormal behaviors consisted of hallucinations, delirious speech, frightening episodes, abrupt anger, abnormal overactivity leading to accidents, and putting unusual objects into the mouth.¹³ Reports from Japan included neuropsychiatric behaviors such as adolescents jumping or falling from balconies. A large number of these falling or jumping adolescents had no premorbid medical or psychiatric history indicating a predisposition to such. Many of these cases involved adolescents.^{9,14}

In the present case, a 15-year-old girl had complained of insomnia, agitation, irritability, and impulsive suicidal ideation from the 3rd day after oseltamivir administration began. This patient developed numerous adverse reactions similar to those reported from Japan. She experienced a depressive episode, lasting 2 months, after receiving oseltamivir treatment for influenza. Unfortunately, we did not receive depression scale score of her depressive episode from the hospital of Thailand. Her school grades greatly dropped below the level she had achieved prior to the onset. We thought that she suffered a de-

pressive episode because she had depressive mood, psychomotor agitation, irritability, insomnia, diminished ability to think or concentrate, recurrent suicidal ideation, and significant impairment in social and academic functioning. We did not consider that she had a bipolar disorder or major depressive disorder because she didn't have a family history of bipolar disorder, major depressive disorder, cyclothymic disorder, or dysthymic disorder and premorbid episode of mood fluctuation or depressive symptom. But it may be possible that her manic symptom was related with antidepressant use. Although it was uncertain, we became assured that her neuropsychiatric symptoms were related with the oseltamivir.

After oral administration, oseltamivir is rapidly absorbed from the gastrointestinal tract and is then extensively metabolized, predominantly by hepatic esterases, into its only active metabolite, oseltamivir carboxylate. Oseltamivir carboxylate is eliminated by a first-order process, primarily through glomerular filtration and renal tubular secretion. Oral oseltamivir at 75 mg twice daily, for 5 days, significantly reduces the duration of naturally-acquired febrile influenza.^{3,4,15,16}

The pharmacological mechanism of the abnormal behaviors observed during oseltamivir administration is unknown. One study showed increased dopamine metabolism changes in the medial prefrontal cortices of rats after systemic oseltamivir administration. The researchers reported that oseltamivir treatment was correlated with the manifestation of abnormal behaviors.¹⁷ Oseltamivir carboxylate can cross the BBB from the blood, but one study showed that its active efflux by brain anion transporters limited its brain distribution. Therefore, these researchers reported that alterations in anion transporters' activities would cause inter-individual variations in exposure to central nervous system and affect the abnormal behaviors.¹⁸ Oseltamivir carboxylate facilitates neuronal firing, though this facilitation does not involve GABAergic disinhibition. This suggests that oseltamivir affects the central nervous system.⁹

However, some researchers suggest it is difficult to distinguish the treatment's effects from those of the disease. Prospective clinical studies found no evidence of a higher incidence of neuropsychiatric events in patients receiving oseltamivir compared to those receiving placebo. These studies support the idea that the disease itself, rather than oseltamivir, more likely causes such neuropsychiatric events.⁷ In the full cohort analysis, influenza patients receiving oseltamivir experienced no increase in neuropsychiatric claims-based events when compared to influenza patients who took no antiviral drugs.¹² Research will have to resolve this debatable issue.

In this patient, who developed prominent neuropsychiatric symptoms immediately after taking oseltamivir, we suggest

that oseltamivir might increase her potential risk for experiencing neuropsychiatric episodes. To our knowledge, this is the first reported case of oseltamivir-associated neuropsychiatric events in South Korea. Although there are many different arguments, we hope our report will lead clinicians to monitor for oseltamivir's potential neuropsychiatric adverse events.

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