Case Report

Oseltamivir-induced Neuropsychiatric Symptoms

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Abstract

Oseltamivir is a viral neuraminidase enzyme inhibitor commonly prescribed for prevention and management of influenza. Common adverse effects of oseltamivir are gastrointestinal side effects such as nausea, vomiting, diarrhea, and pain abdomen; others are headache, insomnia, cough, skin rashes, and sadness. In 2006, US Food and Drug Administration added a warning to the label of oseltamivir drawing attention to the risk of developing neuropsychiatric adverse events (NPAE). However, the incidence of NPAE with oseltamivir has been underreported in India. Hence, in our report, we present the occurrence of neuropsychiatric symptoms such as aggressive behavior, restlessness, hallucinations, paranoid ideas, and insomnia following administration of oseltamivir in a young adult female patient.

Keywords: Adverse drug reaction, Naranjo scale, neuraminidase inhibitor

Introduction

Oseltamivir is a viral neuraminidase enzyme inhibitor commonly prescribed for prevention and management of influenza. It is active against Type A as well as Type B influenza viruses. Oseltamivir is a prodrug which undergoes hydrolysis by hepatic esterases to produce an active metabolite, oseltamivir carboxylate (OCB). Viral neuraminidase enzyme breaks sialic acid components present on the surface of cells infected by virus, thus helping in liberation of progeny virus particles. Inhibition of this enzyme by oseltamivir prevents the propagation of influenza virus. Common adverse effects of oseltamivir are gastrointestinal side effects such as nausea, vomiting, diarrhea, and pain abdomen; others are headache, insomnia, cough, skin rashes, and sadness.[1]

In 2006, US Food and Drug Administration added a warning to the label of oseltamivir drawing attention to the risk of developing neuropsychiatric adverse events (NPAE).[2] The incidence of this condition is very high in Japan. There have been about 100 cases of abnormal behaviors and 70 deaths among children and adolescents in Japan alone.[3] However, the incidence of NPAE with oseltamivir has been underreported in India. Hence, in our report, we present the occurrence of neuropsychiatric symptoms following administration of oseltamivir in a young adult female patient.

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Case Report

A 32-year-old female patient presented to the medicine outpatient clinic of our hospital on May 21, 2017 with chief complaints of fever and cough for 3 days. Her past history revealed no comorbidities; however, she had a normal vaginal delivery without any obstetric complications 2 weeks ago. A thorough physical examination was done. The patient was admitted with a provisional diagnosis of acute febrile illness and influenza. Chest X-ray was taken, blood collected for serology testing (for malaria) and throat swab (for influenza A-H1N1, H3N2 and influenza B), and sputum culture were done. She was started empirically on tablet oseltamivir 75 mg two tablets twice daily along with injection ceftriaxone 2 g intravenously every 12 h, tablet azithromycin 500 mg once a day, and tablet pantoprazole 40 mg once a day before food.

After about 12 h of initiation of oseltamivir, the patient developed aggressive behavior at midnight on the same day, followed by restlessness, hallucinations, paranoid ideas, and insomnia the next day. Urgent psychiatry consultation

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was sought. A single-dose injection haloperidol 10 mg and lorazepam 2 mg slow intravenous stat was recommended and administered. Chest X-ray was normal and throat swab for influenza A (H1N1, H3N2) and influenza B was reported as negative. Influenza as a cause was ruled out. Further, sputum culture revealed no growth after 36 h of incubation, and serology for malaria was negative. A differential diagnosis of postpartum psychosis was also considered but ruled out by psychiatrist. Hence, a diagnosis of oseltamivir-induced neuropsychiatric symptoms was made by the physician after ruling out other causes and oseltamivir was stopped, while continuing the other drugs.

Her psychiatric symptoms along with fever and cough improved the day after oseltamivir was stopped and the patient was discharged. She was later followed up for 2 months, with no neuropsychiatric complaints.

Causality assessment using Naranjo's algorithm[4] resulted in a score of 7 denoting "probable" causality. The presence of documented reports of this reaction, positive temporal association, ruling out possible alternative cause (postpartum psychosis), and presence of an objective evidence (physician confirmation) were considered while calculating the score.

Discussion

Oseltamivir-induced neuropsychiatric adverse effects can be either sudden or delayed onset. Sudden onset reactions, occur within 24 h after initial dose of oseltamivir, are due to direct effects of oseltamivir on central nervous system whereas delayed onset reactions occur after 24 h and are due to effects of OCB.[2,5,6] Till now, most of the oseltamivir-induced neuropsychiatric adverse effects have been reported in Asian population.[5] There are reports from Japan suggesting that patients on oseltamivir experienced neuropsychiatric symptoms such as abnormal behavior, delusions, perceptual disturbances, altered consciousness, delirium, parasomnia, and suicidal events.[3] These side effects occurred mostly in children and younger individuals.[3] A case of mania following 1st day of oseltamivir administration has been reported from China. The patient recovered in a month.[7] In South Korea, an adolescent girl developed depressive symptoms following 3rd day of oseltamivir treatment. The patient's symptoms improved within a month.[3] A similar case was also reported from a male patient in South Korea who developed psychiatric symptoms in the form of mood swings, suicidal feelings, auditory hallucinations, memory deterioration, and insomnia the next day after a 5 day course of oseltamivir. The patient recovered within a week.[8] A 15-year-old girl developed unusual behavior, insomnia, delusions, and visual hallucinations on 2nd day after taking oseltamivir in Japan. The patient recovered after 2 weeks.[9] In all these cases, patients received antipsychotic medication for psychiatric symptoms. Auditory hallucinations were reported after completion of 5-day course of oseltamivir in an 8-year-old girl. She improved after 2 weeks without any antipsychotic medication.[2] Oseltamivir can even worsen the psychiatric symptoms in chronic schizophrenic patients.[10]

Influenza may cause neuropsychiatric symptoms,[5] but in the present case, this was ruled out because the patient's influenza reports were negative. There was no history of previous psychiatric illness. Common form of presentation of postpartum psychiatric illness is depression whereas postpartum psychosis is rare.[11] The present case did not have any depressive episodes, and symptoms did not correspond to features of postpartum psychosis.[11] The absence of risk factors[11] such as past history or family history of bipolar disorder, stress-related factors, obstetric complications, and opinion of the psychiatrist made the diagnosis of postpartum psychosis less likely. Development of symptoms after oseltamivir administration, neuropsychiatric manifestations similar to those reported in earlier studies, and improvement of symptoms after drug withdrawal favor the diagnosis of oseltamivir-induced neuropsychiatric symptoms.

The exact mechanism of oseltamivir-induced psychosis is unknown; however, few postulates have been made. Li *et al*. reported a nonsynonymous single nucleotide polymorphism (SNP), near the active site of human cytosolic sialidase which is a homolog of the virus neuraminidase. This SNP could increase the binding affinity of human sialidase to OCB, thus reducing the sialidase activity. Administration of oseltamivir to such patients (present in 9.29% of Asian population) might reduce the sialidase activity and contribute to the occurrence of severe NPAE.[5] OCB increases neuronal firing and can thus affect central nervous system.[3] Geographic factors, genetic factors, and ethnicity may also play a role in the occurrence of psychiatric symptoms.[8] Another study concluded that administration of oseltamivir by systemic route raised the levels of dopamine and also its metabolic products in the medial prefrontal cortices of rats.[10] Oseltamivir may augment agonist-induced D2 (dopamine) receptor activity. By inhibiting neuraminidase (sialidase), oseltamivir prevents the breakdown of sialic acid linkage to glycolipids. Thereafter, these sialoglycolipids increase the effect of enhanced D2 (Dopamine) receptor activity by agonists.[10] Oseltamivir, in its unchanged form, can produce benzodiazepine-like central depressant action that may result in abnormal behavior, delirium, hallucinations, sleep, and respiratory depression.[12] Mechanisms of delayed onset adverse effects may be associated with inhibition of the endogenous neuraminidase of the host by oseltamivir.[6]

Conclusion

This case signifies that oseltamivir has got a potential to cause and aggravate psychosis. Hence, a close observation and follow-up is necessary while initiating patients on oseltamivir. Caution is also warranted if the patient has coexisting psychiatric illness.

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Conflicts of interest

There are no conflicts of interest.

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