Oseltamivir-Associated Increased Libido in an Influenza B–Infected Adolescent

To the Editor: Oseltamivir is widely used for the treatment of influenza. However, studies[1] have observed adverse neuropsychiatric effects, including behavioral changes and perceptional disturbance, in oseltamivir-treated patients. We report the case of a patient who exhibited an increased libido and irregular behavior after treatment with oseltamivir. Increased dopamine levels might partially explain these behavioral changes. Physicians must consider the possibility of behavioral changes in high-risk patients before prescribing oseltamivir.

Case report. A 15-year-old boy with no developmental delay or psychiatric disorder had experienced a nonproductive cough and fatigue for 4 days. Due to exacerbating symptoms and drowsy consciousness within 2 days, he was sent to the Taipei Medical University Hospital emergency room. Influenza B infection was confirmed through an influenza rapid test. The patient also suffered from hypoxemia and bradycardia during this period. Oseltamivir phosphate (Tamiflu) (in 75-mg capsules) was prescribed immediately. There was no other medication used at that time. After treatment, his vital signs and consciousness stabilized, and he was transferred to a general pediatric ward.

On day 1 in the general pediatric ward, the patient presented with clear consciousness and afebrility; his blood pressure, complete blood count, C-reactive protein level, cardiac enzyme level, and liver function test results were all within reference ranges. The physical and neurologic examination showed no abnormal findings. The patient was orally administered oseltamivir phosphate in 75-mg capsules every 12 hours.

On day 2, although his vital signs and neurologic function remained stable, he presented with symptoms of blunted affect, irritability, and speech repetition. We discontinued the oseltamivir treatment to prevent additional adverse effects. Overall, the patient had received four 75-mg oseltamivir capsules. Brain magnetic resonance imaging (MRI) with contrast was arranged to eliminate acute disseminated encephalomyelitis and showed no abnormal findings. However, symptoms of apathy, lack of eye contact, and slow reaction to any stimulus persisted. The patient's parents refused additional invasive procedures, such as a lumbar puncture.

On day 4, the patient became impulsive and irritable and demonstrated an increased libido, such as grabbing the nurses and persistently requesting sexual intercourse. His orientation, calculation ability, memory, and abstract thinking were preserved; however, he exhibited fear of surroundings and feelings of derealization and detachment. The electroencephalogram revealed diffuse cortical dysfunction. No psychiatric medication was prescribed at that time. On day 6, the patient's mental status showed gradual improvement. The patient was discharged with no psychiatric medication.

Oseltamivir is an effective and tolerated antiviral drug that is widely approved for the treatment and prophylaxis of influenza in children aged 1 to 12 years.[1] Although several studies[2–6] have reported adverse neuropsychiatric effects related to oseltamivir treatment, this finding was not consistent. A systematic review[7] reported psychiatric adverse effects after oseltamivir treatment included nervousness, aggression, hallucinations, psychosis, suicide ideation, and paranoia. In addition, in Toovey et al,[6] oseltamivir-exposed influenza patients were not associated with any increase in claims-based neuropsychiatric events compared to patients not treated with oseltamivir.

The assessment of neuropsychiatric events associated with the use of oseltamivir in patients with influenza infection is problematic because the possibility of concomitant influenza-induced encephalopathy cannot be excluded.[5,6] Our patient's MRI with contrast showed no evidence of encephalopathy, and he exhibited no changes in consciousness or orientation or signs of central nervous system (CNS) infection. The medical staff observed that his behavioral changes started after he received 4 oseltamivir doses. Oseltamivir was the only medication prescribed at that time. This patient received no other medication for symptom relief that might result in abnormal behavior. His electroencephalogram revealed diffuse cortical dysfunction. For 5 days, the patient displayed symptoms of persistent derealization, an increased libido, and sexual impulsive behavior despite the discontinuation of oseltamivir treatment. However, after day 6, his physical condition, mental status, and behavior returned to previous levels with no need for psychiatric medication.

There are several possible mechanisms of these psychiatric adverse reactions. Hiasa et al[8] demonstrated that oseltamivir inhibits monoamine oxidase A, which degrades dopamine, and causes abnormal behaviors in mice. Yoshino et al[9] further demonstrated that oseltamivir increased dopamine levels in the medial prefrontal cortex of rats. These results[8,9] and our report indicate that dopaminergic pathways might regulate copulation, genital reflexes, and libido. Oseltamivir is metabolized to oseltamivir carboxylate (OCB), which is a neuraminidase inhibitor. OCB might play a role in CNS development and impulse conduction. One study[10] found that in the hippocampal slices of oseltamivir- and OCB-exposed juvenile rats, OCB caused adverse effects in the rat CNS due to the immature and impaired blood-brain barrier. Other evidence[11] showed that nicotinic acetylcholine, which is inhibited by oseltamivir, affects the CNS.

In addition, there are 2 types of neuropsychiatric reaction: sudden-onset type and delayed-onset type.[12] This case should be classified as delayed-onset type because 4 doses (at least 2 days) was needed to induce reactions in the patient. These psychiatric symptoms, which occurred in the late phase of treatment after prolonged duration, may also be due to oseltamivir.

To our knowledge, this is the first report of increased libido in response to oseltamivir treatment. We advise that clinicians carefully monitor adolescent male patients for an increased libido and related behavioral changes because of potential negative effects on medical staff. Further research to investigate the mechanisms underlying the association between oseltamivir treatment and an increased libido is warranted.

References

1. Newland JG, Romero JR, Varman M, et al. Encephalitis associated with influenza B virus infection in 2 children and a review of the literature. *Clin Infect Dis*. 2003;36(7):e87–e95.
2. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.
3. Studahl M. Influenza virus and CNS manifestations. *J Clin Virol*. 2003;28(3):225–232.
4. Tanabe T, Hara K, Nakajima M, et al. Oseltamivir treatment for children showing abnormal behavior during influenza virus infection. *Brain Dev*. 2010;32(6):440–444.
5. Smith JR, Sacks S. Incidence of neuropsychiatric adverse events in influenza patients treated with oseltamivir or no antiviral treatment. *Int J Clin Pract*. 2009;63(4):596–605.
6. Toovey S, Rayner C, Prinssen E, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. *Drug Saf*. 2008;31(12):1097–1114.
7. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database Syst Rev*. 2014;(4):CD008965.

8. Hiasa M, Isoda Y, Kishimoto Y, et al. Inhibition of MAO-A and stimulation of behavioral activities in mice by the inactive prodrug form of the anti-influenza agent oseltamivir. *Br J Pharmacol*. 2013;169(1):115–129.
9. Yoshino T, Nisijima L, Shioda K, et al. Oseltamivir (Tamiflu) increases dopamine levels in the rat medial prefrontal cortex. *Neurosci Lett*. 2008;438(1):67–69.
10. Izumi Y, Tokuda K, O'dell KA, et al. Neuroexcitatory actions of Tamiflu and its carboxylate metabolite. *Neurosci Lett*. 2007;426(1):54–58.
11. Muraki K, Hatano N, Suzuki H, et al. Oseltamivir blocks human neuronal nicotinic acetylcholine receptor-mediated currents. *Basic Clin Pharmacol Toxicol*. 2015;116(2):87–95.
12. Hama R. The mechanisms of delayed-onset type adverse reactions to oseltamivir. *Infect Di Lond)s*. 2016;48(9):651–660.

Yu-Jui Huang, MD[a]
Shih-Yun Lin, MD[a]
Kuo-Hsuan Chung, MD[a,b,c]
ch2006ung@tmu.edu.tw
Hsi Chang, MD[d]

[a]Department of Psychiatry, Taipei Medical University Hospital, Taipei, Taiwan
[b]Psychiatric Research Center, Taipei Medical University Hospital, Taipei, Taiwan
[c]Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[d]Department of Pediatrics, Taipei Medical University Hospital, Taipei, Taiwan

Potential conflicts of interest: None.

Funding/support: None.

Additional information: The information was de-identified to protect patient anonymity.

Published online: May 10, 2018.

Prim Care Companion CNS Disord 2018;20(3):17l02175

To cite: Huang Y-J, Lin S-Y, Chung K-H, et al. Oseltamivir-associated increased libido in an influenza B–infected adolescent. *Prim Care Companion CNS Disord.* 2018;20(3):17l02175.

To share: https://doi.org/10.4088/PCC.17l02175