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CASE REPORT

Oseltamivir and Neuropsychiatric Behaviors – A Case Report on an Adolescent Teen and Evaluation of the Literature

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Abstract:
Objective: To illustrate a case of oseltamivir induced neuropsychiatric behaviors in an adolescent teen.
Case Summary: A 15-year-old previously healthy adolescent presented to the emergency department with acute onset of altered mental status after taking two doses of oseltamivir prescribed to him by his primary care physician for presumed influenza infection. A thorough examination at the hospital, which included a urine drug screen, complete blood count, complete metabolic panel, urine and blood cultures, head computed tomography, and chest radiograph, did not indicate any other clinical conditions that could explain his abnormal behaviors. No other medications were given to him in the hospital. About 20 hours after the last dose of oseltamivir, he awoke from a nap and his mental status was completely back to baseline. He had no memory of the events transpired in the past 24 hours and was discharged home with no further incidence.
Disscusion: Oseltamivir is an anti-viral agent that is often used as treatment and prophylaxis for influenza infection. Neuropsychiatric adverse events such as hallucination and delirium can potentially occur with this agent. This rare adverse event may be due to the binding of the medication to the enzyme sialidase causing increase in dopamine activity. Most of the reports were in young Japanese children less than 16 years old. Some studies have shown a causal relationship with oseltamivir leading to this adverse event, while some have failed to do so, probably due to flaws in their analytical method. The Naranjo ADR probability scale showed a possible causality between neuropsychiatric behaviors and oseltamivir administration in this patient.
Conclusions: Oseltamivir is an effective anti-viral for influenza infection if started early in the course of the illness. Clinicians should monitor for neuropsychiatric symptoms when starting patients on this medication.

Key words: *oseltamivir, neuropsychiatric, pediatric, influenza*
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Introduction

Oseltamivir is an antiviral agent that has been mentioned a lot recently in both the public and the healthcare setting due to the advent of the H1N1 influenza virus. It is an effective medication that targets both influenza A and B viruses. When this medication was first approved by the United States Federal Drug Administration (FDA), it was not indicated in pediatric patients less than 1 year of age due to the lack of data in this age group [1]. One of the concerns with infants taking this medication is the development of gasping syndrome [2]. but because of the severity of the H1N1 virus, the FDA has conducted an emergency review on oseltamivir this year and has approved it to be used in both infants and neonates [3,4]. Besides gasping syndrome, oseltamivir can also cause other adverse events, one being neuropsychiatric behaviors [1]. The following case will illustrate this rare but potential deadly adverse event.

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Case Report

A 15-year-old previously well Caucasian male (87kg) presented to the emergency department (ED) with acute onset of altered mental status. He had been acting normally the evening prior to his symptoms, though he had two days of malaise, cough, runny nose, fever, chills, and headache. His primary care physician had prescribed oseltamivir empirically for probable influenza the day prior to his presentation. At about 2 a.m. he awoke screaming nonsensically. He had a fever of 103 F and was given ibuprofen by his mother. Upon arrival to the ED he was inappropriately laughing and grabbing at the air. He had no neck stiffness, had a normal gait, normal coordination, normal strength, and his cranial nerves were normal. His white blood cell count was 3.6 K/uL (4.5-13.5), and his hemoglobin, platelets, and complete metabolic panel were normal. A chest x-ray was obtained, and no acute cardiopulmonary process was found. A head computed tomography was also normal showing no intracranial bleed. His urine drug screen was negative, and his acetaminophen and salicylate level were within normal limit. A urinalysis was performed and it was essentially normal with a specific gravity of 1.022 (1.005-1.030). His past medical history was unremarkable and his immunizations were up to date. His only medications were acetaminophen and ibuprofen for fever, loratadine for allergic rhinitis, and two doses of oseltamivir, the last of which was taken about six hours prior to the onset of symptoms. He was admitted to the pediatric inpatient service for observation and his fever resolved, though he continued to have altered mentation. His heart rate was between 60-70, respirations 20-25, and his blood pressures were normal. About 20 hours after the last dose of oseltamivir, he awoke from a nap and was completely back to baseline. He was oriented to person, place, and time but had no memory of the past 24 hours. He was discharged home without incident. His blood culture was negative after 5 days and his urine culture was also negative. A reverse transcriptase-polymerase chain reaction (rRT-PCR) for H1N1 influenza was positive.

Discussion

Oseltamivir is an antiviral agent that has recently been used more often in the healthcare setting due to the recent advent of the swine (H1N1) influenza virus. Oseltamivir is a neuraminidase inhibitor similar to the inhaled agent zanamavir that prevents the shredding of virions from the infected cells leading to cessation of virus' spread and proliferation [1]. Over the years, concerns have been raised regarding the side effects profile of this antiviral agent and its safety in the pediatric population. A few years ago, the FDA did not approve oseltamivir to be used in infants less than 1 year old due to the lack of evidence in this population. Also, there are concerns for gasping syndrome, a condition that can potentially develop by ingesting large amount of sodium benzoate (one of the inactive ingredients in the oseltamivir suspension formulation) [1]. Infants with gasping syndrome can present with respiratory and neurological signs requiring immediate medical attention [2]. Due to the prevalence and virulence of the H1N1 virus, however, the FDA has performed an emergency use authorization review on oseltamivir[3] and loosened its restriction on giving this medication to infants less than one year old [4].

Besides gasping syndrome, oseltamivir is also known for its neuropsychiatric adverse effects. In fact, neuropsychiatric symptoms like delirium and hallucination are listed as potential adverse effects in the package insert by the manufacturer (Roche®).[1] Our case illustrates this rare adverse effect and has fulfilled the Naranjo ADR probability scale, showing a possible causality between oseltamivir and the development of abnormal behaviors [5].

Most of the cases of neuropsychiatric adverse events were observed in younger children $\leq$ 16 years old and mostly reported in Japan, where the majority of the oseltamivir was dispensed [6]. The prevalence of such adverse events is not known in the adult population; there was only one case report that we could find describing oseltamivir-induced delirium in a geriatric patient. This particular patient was reported to have a history of vascular dementia but was clinically stable. Within 2 days after starting on 75mg of daily oseltamivir, she developed aggression and extreme confusion requiring psychiatric hospitalization. Her mental status returned to baseline after discontinuation of the offending agent [7].

To our knowledge, this case report is the first to be published describing the neuropsychiatric adverse effects associated with oseltamivir in an American adolescent. According to the literature, the neuropsychiatric behaviors associated with oseltamivir are usually observed within the first day after starting on the medication,[8] which coincides the onset of symptoms experienced by our case patient. Such symptoms can consist of, but are not limited to, aggressive temper, fright, anger, hallucination, ingesting objects, and other strange behaviors leading to self-bodily harm.[9,10] As seen in our patient, these symptoms usually resolve with discontinuation of the offending agent. It took our patient nearly 24 hours to recover from the adverse event, which may relate to the half life of oseltamivir phosphate (1 – 3 hours) and the active metabolite oseltamivir carboxylate (6 – 10 hours) [1].

In 2007, the Japanese Ministry of Health reported 22 suicides (fall or jump) that were associated with

oseltamivir, of which approximately 70% were in children between 10 and 19 years old. Because of this report, the Japanese governmental agency issued a warning to clinicians about prescribing oseltamivir to patients in this age group [6].

One year prior to this recommendation by the Japanese Ministry of Health, the Pediatric Advisory Committee of the FDA noted that there were increasing reports of neuropsychiatric adverse effects in pediatric patients worldwide who had taken oseltamivir compared to the incidence between 1999 and early 2005. This trend could not be easily explained because the incidence of influenza did not increase and the strands of the virus did not mutate during this period of time. The prescribing rate of oseltamivir also did not increase; in fact, oseltamivir prescriptions reduced by about 30% in Japan during this time period.[11] Because of this unexplained phenomenon, Roche tried to investigate the cause of this increase in the reporting rate. They looked at their clinical studies, available literature, and post-marketing adverse events reporting. They sought to determine if there was any difference in the incidence of neuropsychiatric adverse events between the patients who took oseltamivir and those who did not, to find out how much of the oseltamivir compound and its metabolites can go into the central nervous system and exhibit pharmacological activities, and to evaluate if there are any pharmacogenomic differences between ethnicities (mainly Caucasians and Japanese) that could explain the difference in incidence of the adverse events. In their investigation, they did not find any difference in the incidence between the patients who took oseltamivir and those who did not. In addition, they noted that the brain has about a 20% lower concentration of the compound compared with the plasma, and there is a limited amount of oseltamivir being converted to the active metabolite oseltamivir carboxylate in the brain. Finally, they were not able to find any genetic difference between the Japanese and the Caucasians which could explain the difference in reporting rates between these two ethnicities.[12] Some clinicians attribute the neuropsychiatric symptoms that patients experience after taking oseltamivir to the influenza infection itself. Influenza or fever can sometimes lead to abnormal behaviors in children.[13] In one report by Wang and colleagues, a child developed psychosis from influenza without administration of oseltamivir [14].

Besides this Roche-sponsored study, there were two other studies performed by the Japanese that showed no significant association between the intake of oseltamivir and neuropsychiatric behaviors.[9,15,16] The first was a surveillance study by Yokota and colleagues on about 2800 children. They found that some patients developed abnormal behaviors after the first day of being on oseltamivir, but their findings were not statistically significant.[15] Of note, the main researcher of this study received US $85,000 from the distributor of oseltamivir in Japan around that time.[17]

The second study was an observational cohort consisting of 10,000 Japanese children infected with influenza virus from 692 institutions who were put on oseltamivir. Questionnaires about neuropsychiatric behaviors were completed by both the patients' family and the physicians. Twelve percent of the prescribed group developed abnormal behaviors, whereas 13% of the patients from the non-prescribed group had the same symptoms, resulting in an insignificant risk ratio of 0.93 (0.82 – 1.05).[9.16] Another researcher re-evaluated this study and found that the particular statistical method that they originally used was flawed. After re-analyzing the data using person-time method, the risk ratio was found to be 1.57 (1.34 – 1.83), indicating that Japanese children on oseltamivir were about one and a half times more likely than oseltamivir-naïve Japanese children to develop abnormal neuropsychiatric behaviors [9].

The mechanism behind the development of these abnormal behaviors is not fully understood, but researchers hypothesize that it may be due to the stimulation of dopamine D2 receptors by oseltamivir. In a mouse in-vitro study, the activity of D2 receptors was stimulated by an increased amount of serum sialoglycoplids in the mouse. Oseltamivir can bring about this reaction by sialyating serum glycolipid.[18] However, further study in human needs to validate this hypothesis.

Even though the Roche-sponsored study did not find any pharmacogenomic reason to explain the difference in reporting rate among the Japanese and other racial groups (i.e. Caucasians), a recent study by Li and colleagues may explain this phenomenon.[19] This research group found a nonsynonymous single nucleotide polymorphism (SNP) in human cytosolic sialidase that is more prevalent in Asians. This polymorphism can increase the binding affinity of oseltamivir to the sialidase, a homologue to neuraminidase. This binding can reduce the activity of sialidase, which is hypothesized to cause neuropsychiatric adverse events in patients on oseltamivir. Per the researchers, people with congenital sialidase deficiency syndrome can also present with neurological symptoms; however, their symptoms are not similar to those associated with oseltamivir intake [19].

Regardless of the mechanisms behind the development of neuropsychiatric adverse effects with oseltamivir, such side effects can potentially lead to unfavorable outcomes. In a recent cross-sectional study performed in London, adherence to oseltamivir was

assessed in 103 children.[20] Of these respondents, only 50% primary school children and about 75% secondary school children completed the full course of the medication. The main reason for non-compliance was intolerable side effects, of which approximately 20% were related to neuropsychiatric behaviors. Non-adherence to oseltamivir can potentially lead to resistance of the H1N1 virus, which can be detrimental.

Conclusion

Oseltamivir can be an effective anti-viral agent for treating influenza virus if started early in the course of the illness. There is still much that we as clinicians do not understand about the use of oseltamivir in the pediatric population. For example, we still do not know what specific adverse events can occur in children and whether different adverse events can manifest in different age groups. Also, we really do not have a good idea of how to dose this medication in the neonatal population due to lack of pharmacokinetic data in this age group. In order to prevent potential life-threatening adverse events, more investigations and clinical studies need to be performed to help us better understand the pharmacokinetic, pharmacodynamic, and therapeutic properties of oseltamivir in pediatrics. In the meantime, clinicians need to monitor their patients closely for adverse effects, especially neuropsychiatric symptoms, when they are put on this anti-viral medication.

REFERENCES

1. Roche Laboratories Inc. Tamiflu prescribing information, August 2008 [online]. Available from URL:http://www.gene.com/gene/products/information/tamiflu/pdf/pi.pdf [Accessed 2009 Oct 23]

2. Gershanik J, Boecler B, Ensley H, et al. The gasping syndrome and benzyl alcohol poisoning. NEJM 1982;307:1384-8

3. US FDA. Emergency use authorization (EUA) review oseltamivir phosphate for swine influenza A, September 2009 [online]. Available from URL: http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM153547.pdf [Accessed 2009 Oct 23]

4. US FDA. Emergency use of Tamiflu in infants less than 1 year of age: postmarket drug safety information for patients and providers, 25 September, 2009 [online]. Available from URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm183870.htm [Accessed 2009 Oct 23]

5. Naranjo CA, Busto U, Sellers EM, et al. A method to estimate the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics 1981;30:239-45

6. Terada K, Kawai Y, Monju A, et al. Adolescent jump case in Japan associated with influenza but not oseltamivir. Pediatr Infect Dis J 2008;27:88-9

7. Kohen I. Oseltamivir-induced delirium in a geriatric patient. Int J Geriatr Psychiatry 2007;22:930-6

8. Hama R. Fatal neuropsychiatric adverse reactions to oseltamivir: Case series and overview of causal relationships. Int J Risk Safety Med 2008;20:5-36

9. Yorifuji T, Suzuki E, Tsuda T. Oseltamivir and abnormal behaviors: True or not? Epdiemiology 2009;20:619-21

10. Oseltamivir: cutaneous and neurological adverse effects in children. Prescrire Int 2006;15:182-3

11. Toovey S, Rayner C, Prinssen E, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. Drug Safety 2008;31:1097-1114

12. US FDA. Meeting of the FDA Pediatric Advisory Committee, 27 November 2007 [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4325t1_transcript.pdf [Accessed 2009 Oct 23]

13. Hara K, Tanabe T, Nakano R, et al. Clinical characteristics of children with abnormal behaviors associated with influenza infection. J Jpn Pediatr Soc 2007;111:38-44

14. Wang YH, Huang YC, Chang LY, et al. Clinical characteristics of children with influenza A virus infection requiring hospitalization. J Microbiol Immunol Infect 2003;36:111-6

15. Yokota S. Investigations about the frequency of associated symptoms with influenza [in Japanese], 20 October 2008 [online]. Available from URL: http://www.mhlw.go.jp/topics/2006/10/dl/tp1020-2.pdf [Accessed 2009 Oct 23]

16. Hirota Y. Interim report of investigations about the frequency of associated symptoms with influenza [in Japanese], 10 July 2008 [online]. Available from URL: http://www.mhlw.go.jp/shingi/2008/07/dl/s0710-6ak.pdf [Accessed 2009 Oct 23]

17. New concerns about oseltamivir. Lancet 2007;369:1056

18. Suzuki M, Masuda Y. Effect of a neuraminidase inhibitor (oseltamivir) on mouse jump-down behavior via stimulation of dopamine receptors. Biomed Res 2008;29:233-8

19. Li CY, Yu Q, Ye ZQ, et al. A nonsynonymous SNP in human cytosolic sialidase in a small Asian population results in reduced enzyme activity: potential link with severe adverse reactions to oseltamivir. Cell Res 2007;17:357-62

20. Kitching A, Roche A, Balasegaram S, et al. Oseltamivir adherence and side effects among children

in three London schools affected by influenza A (H1N1)v, May 2009 – an internet-based cross-sectional survey. Euro Surveill 2009;14:19287