Possible Neuropsychiatric Reaction to High-Dose Oseltamivir during Acute 2009 H1N1 Influenza A Infection

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The safety of high-dose oseltamivir during treatment of 2009 H1N1 influenza A infection for critically ill patients is unknown. Here we report on a case patient with severe, delayed-onset neuropsychiatric symptoms after administration of high-dose oseltamivir. Clinicians should be vigilant to the possible increased risk of complications associated with high-dose oseltamivir therapy for 2009 H1N1 influenza A infection.

Oseltamivir is widely prescribed to prevent and treat influenza infection [1, 2]. During the present 2009 H1N1 influenza A pandemic, increased oseltamivir use is expected, and clinicians may administer higher doses to critically ill patients on the basis of expert recommendations [3]. Neurologic complications have been attributed to infection with influenza A and B viruses [4] and, more recently, to infection with 2009 H1N1 influenza A virus [5]. Sudden- and delayed-onset adverse neuropsychiatric reactions to oseltamivir have also been reported after standard and high dosing for patients infected with influenza, resulting in several deaths [6–8].

Case report. In July 2009, a previously high-functioning 43-year-old Vietnamese man developed a fever, cough, and sinus congestion 4 days after undergoing an autologous stem cell transplant for acute promyelocytic leukemia. Computed tomography scans of the chest and sinuses revealed ground-glass opacities throughout the lungs and bilateral mastoid and sphenoid sinus opacification consistent with pneumonia and sinusitis, respectively. On day 6 after the onset of fever, a direct fluorescent-antibody assay of respiratory viruses was positive for influenza A virus, which was later subtyped as novel 2009 H1N1. High-dose oseltamivir (150 mg orally twice daily) was started on the evening of day 6 after onset of fever. On day 8 after onset of fever, the patient became disoriented in time and place, had visual hallucinations, and was transferred to the intensive care unit for closer monitoring. Arterial blood gases, electrolytes, and renal function were normal, blood and urine cultures were negative, and review of his other medications (cefepime, acyclovir, entecavir, filgrastim, heparin, pantoprazole, docusate, and senna) failed to reveal any likely cause of his altered mental status. Neuroimaging was not obtained because of his inability to lay still for the study, and a lumbar puncture was not performed because of thrombocytopenia.

Because of the temporal association between altered mental status and initiation of oseltamivir, investigation for possible oseltamivir-induced neurotoxicity was initiated. Plasma concentrations of unchanged oseltamivir and its active metabolite, oseltamivir carboxylate, were measured (Figure 1), and oseltamivir was discontinued. Although the patient remained febrile and hypoxic, his mental status returned to baseline within 24 h after oseltamivir therapy was discontinued, consistent with the decline in plasma oseltamivir carboxylate concentrations. Treatment with standard-dose oseltamivir (75 mg orally twice daily) was started on day 10 after onset of fever and elicited no further neuropsychiatric complications.

The patient’s hospital course was complicated by persistent fever, hypoxia, neutropenia, and delayed stem cell engraftment. Respiratory samples remained positive for influenza A, which was determined by use of polymerase chain reaction (PCR), on days 9, 19, and 31 after onset of fever. The patient’s fever resolved 42 days after onset. On day 49 after onset of fever, oseltamivir was discontinued after repeat PCR testing for influenza virus resulted in a negative test result, and stem cell engraftment occurred. He was discharged on day 62 after onset of fever.

Methods. Clinical data were gathered from the electronic medical record and nursing medication administration record. A direct fluorescent-antigen assay (Millipore) and PCR (Luminex) were used to detect the following respiratory viruses: metapneumovirus, rhinovirus, influenza A subtypes H1 and H3, influenza B, respiratory syncytial virus subtypes A and B, parainfluenza 1, 2, and 3, and adenovirus. Novel 2009 H1N1 influenza A virus was confirmed by the California State Public...
was the sampled time points, except the third time point, which of oseltamivir carboxylate to oseltamivir was estimated at 1 × 10⁻⁸. Serum was collected without an esterase inhibitor, kept on ice until prompt cryopreservation and Characterization Panel. Serum was collected without an esterase inhibitor, kept on ice until prompt cryopreservation and Characterization Panel. Consent for publication in print and electronically was obtained from the patient. Consent for publication in print and electronically was obtained from the patient.

Results. Measured levels of oseltamivir carboxylate were consistent with those expected during treatment with oseltamivir 150 mg by mouth twice daily [9]. The peak levels correlated with the onset and duration of acute neuropsychiatric symptoms, and shortly after discontinuation of oseltamivir, the neuropsychiatric symptoms resolved (Figure 1). The concentration of oseltamivir was below the lower limit of detection (0.25 ng/mL) at all time points except for the first time point (<1 ng/mL) and third time point (5.03 ng/mL). The ratio of oseltamivir carboxylate to oseltamivir was estimated at >50 at the sampled time points, except the third time point, which was ~10 [10], suggesting that, despite the omission of an esterase inhibitor during specimen collection, oseltamivir carboxylate concentrations were only marginally affected by ex vivo conversion.

Discussion. Oseltamivir may have contributed to the altered mental status in this patient with acute 2009 H1N1 influenza A infection. The neuropsychiatric symptoms resolved once oseltamivir carboxylate concentrations had declined to levels consistent with standard-dose oseltamivir (300 ng/mL) [9]. The independent association of influenza with neuropsychiatric complications confounds the establishment of direct causality in suspected cases of oseltamivir neurotoxicity. However, in a prior influenza epidemic, neurological complications were reported predominantly within 48 h of illness onset, and 4 children (age range, 7–17 years) with neurological complications attributed to 2009 H1N1 influenza A infection were reported to have experienced neurological symptoms a median of 1.5 days (range, 1–4 days) from onset of respiratory symptoms [4, 5]. Our patient developed neurological symptoms 8 days after onset of fever and respiratory symptoms, which is not consistent with the time course of neurological complications of influenza in other reports. Other possible explanations for his altered mental status, such as secondary infection, hypoxia, or drug toxicity, did not correlate temporally with the clinical course. Review of the patient’s medication history for possible medication interaction with the metabolism or clearance of oseltamivir also revealed no likely causes.

Although several postmarketing assessments of adverse neuropsychiatric events with oseltamivir have not yielded a significant causal relationship [11, 12], neuropsychiatric disorders due to oseltamivir have been reported to the US Food and Drug Administration and other regulatory agencies [6–8]. Reported oseltamivir-associated neuropsychiatric reactions have been both sudden and delayed onset. Our patient evidently had a delayed-onset adverse reaction to oseltamivir, for which oseltamivir carboxylate appears to be the relevant mediator [6, 13]. In contrast, sudden-onset adverse reaction, shortly after the first dose, is thought to be caused by direct effects on the central nervous system by oseltamivir. As expected, we did not find significant levels of oseltamivir given the rapid, in vivo conversion of oseltamivir to oseltamivir carboxylate and the absence of an esterase inhibitor during specimen collection.

The majority of reported neuropsychiatric events during oseltamivir therapy, including our case, occur in acutely ill patients of Asian descent. Many Asians carry a nonsynonymous single nucleotide polymorphism in the cytosolic sialidase HsNEU2, a homologue of the viral neuraminidase targeted by oseltamivir carboxylate [14]. Such a variant increases binding of oseltamivir carboxylate to human sialidase, further reducing its activity, and may participate in the mechanism for delayed-onset adverse reactions to oseltamivir [6].

Our patient subsequently tolerated standard-dose oseltamivir after recovery from his neuropsychiatric adverse reaction. Decreasing hypercytokinemia, which is required for oseltamivir to penetrate the blood-brain barrier [7], may also have been involved in his improvement in mental status. However, this seems less likely, because the patient’s influenza infection worsened and his respiratory disease progressed despite resolution of his altered mental status.

High-dose oseltamivir has been recommended by some ex-
experts for the treatment of influenza infection in severely ill patients [3]. This dose has been considered safe [9, 15, 16], but this case shows that clinicians must balance the potential benefit of high-dose oseltamivir against the possible increased risk of complications in acute 2009 H1N1 influenza A infection. In conclusion, high-dose oseltamivir may cause neuropsychiatric reactions. Further investigation is required to establish direct causality and the mechanism of toxicity.

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References