Oseltamivir use in infants under one year of age: are there still unanswered questions?

Ateş Kara[1], Eda Karadağ-Öncel[1], Aslınur Özkaya-Parlakay[1], Gülay Korukluoğlu[2], Arzu Bağdat[1], Melda Çelik[1], Mehmet Ceyhan[1], Ali Bülent Cengiz[1]

[1]Division of Pediatric Infectious Diseases, Department of Pediatrics, Hacettepe University Faculty of Medicine, and [2]Refik Saydam Center of Hygiene and Disease Control, Ankara, Turkey

SUMMARY: Kara A, Karadağ-Öncel E, Özkaya-Parlakay A, Korukluoğlu G, Bağdat A, Çelik M, Ceyhan M, Cengiz AB. Oseltamivir use in infants under one year of age: are there still unanswered questions? Turk J Pediatr 2012; 54: 25-29.

The influenza A (H1N1) virus responsible for the 2009 pandemic follows a more severe course in children, thus increasing the need for hospitalization. On the other hand, during the first weeks of the pandemic, use of oseltamivir (Tamiflu®) in children was restricted, and it was not yet approved for use in children younger than one year of age because of the lack of adequate safety and efficacy data and because of concerns regarding central nervous system (CNS) toxicity in newborn rats. However, citing a state of emergency, conditional approval was granted first in the United States, then Europe and finally in Turkey. The main aim of this study was to share our experience with oseltamivir in 35 patients less than one year of age during the 2009 H1N1 pandemic. A total of 35 infants (21 boys, 14 girls; mean age: 160 days [24-335]) were treated during the study period. Six patients required hospitalization, five of whom (14.2%) had an underlying chronic disorder. During the pandemic, we diagnosed H1N1 infection based on clinical symptoms. Nasal swabs were positive for H1N1 in 88.5% of cases. Mild elevations in liver enzymes were present in 39.1% of patients with available blood work-up at presentation, and no changes in liver enzymes were observed with oseltamivir treatment. None of the patients developed any neurological, dermatological or gastrointestinal side effects in association with oseltamivir treatment. No complaints of drowsiness, lethargy or sleep disturbance were reported by the parents. Although our case number is very limited, our study results suggest that oseltamivir is well tolerated in young infants, and we can conclude that oseltamivir could be used in the treatment of influenza A in this age group. Nevertheless, further studies are needed to evaluate using oseltamivir in more cases among infancy age groups.

Key words: oseltamivir, adverse events, infants, H1N1.

The influenza virus is known to result in an acute respiratory infection with significant morbidity and mortality[1,2]. In the fall of 2009, many people from both the northern and southern hemispheres were affected by the influenza A (H1N1) pandemic. The H1N1 strain of 2009 differed from previous strains in that infections followed a more severe course in children, with a higher frequency of complications requiring hospitalization[3]. The neuraminidase inhibitors oseltamivir (Tamiflu®) and zanamivir (Relenza®) were the two antivirals used to treat the 2009 H1N1 pandemic. However, before the pandemic influenza, the use of both drugs was associated with several restrictions, particularly age[4]. Initially, the prophylactic and therapeutic use of oseltamivir was not recommended for patients less than one year of age, while recommendations for zanamivir included a minimum age of seven years for therapeutic use and a minimum age of five years for prophylactic use[3]. Oseltamivir was not recommended under one year of age because of the neuropsychiatric adverse events, especially in Japanese infants. Oseltamivir use was associated with a high rate of neurological conditions like delirium, abnormal behavior, hallucinations, convulsions, and encephalopathy. On the other hand, infants

under one year of age are more susceptible to influenza-associated encephalopathy than older children[5]. Considering these adverse event reports, the use of oseltamivir was restricted for infancy due to safety concerns. However, by April 2009, the United States-based Food and Drug Administration (FDA) approved the use of oseltamivir in infants younger than one year of age for pandemic influenza[6]. However, today, data on the use of this drug in young infants and its side effect profile are still limited. The goal of this study was therefore to share and evaluate the adverse effect profile associated with oseltamivir use in infants.

Material and Methods

Infants younger than one year of age who presented to the Infectious Diseases outpatient clinic at Hacettepe University İhsan Doğramacı Children's Hospital between 28 October 2009 and 30 December 2009 with flu-like symptoms (fever, cough, nasal discharge and blockage, breathing difficulty) and who were treated with oseltamivir were evaluated. Information regarding age, gender, time to presentation after onset of symptoms, presenting complaints, disease complications, comorbid conditions, results of laboratory work-up on presentation, and adverse effects of antiviral therapy was collected.

During the pandemic, a standard protocol was followed by our hospital, which required the patients to attend follow-up visits on the 3rd and 5th day of the treatment, with the aim of ensuring patient compliance and monitoring side effects. For patients who could not be brought to the hospital, parents were contacted by telephone. As per protocol, nasal swabs were obtained for all patients to be tested for real-time reverse transcriptase polymerase chain reaction (RT-PCR) specific to 2009 H1N1 at the Refik Saydam National Public Health Agency. All patients were given oseltamivir (2 doses at a dose of 3 mg/kg/dose for 5 days)[3,6].

Results

The complete records of 35 patients who were treated with antiviral therapy during the study period could be retrieved for analysis. RT-PCR results of nasal swabs were positive in 31 (88.5%) patients. The mean age of patients was 160 (min: 24 - max: 335) days, and 21 (60%) were male and 14 (40%) were female. Four (11.4%) of these patients were <3 months, 13 (37.1%) were 3-5 months, 10 (28.5%) were 6-9 months, and 8 (22.8%) were 10-12 months of age.

With regard to presenting symptoms, 32 patients (91.4%) had fever, 27 (77.1%) had nasal discharge-blockage, 31 (88.5%) had a cough, and 14 (40%) had breathing difficulties (Table I). The mean time to presentation in our patient population was 2 days. A total of 6 patients (17.1%) required hospitalization, 5 of whom had an underlying comorbid condition (2 congenital heart disorder, 1 prematurity, 1 Hirschsprung disease, 1 progressive metabolic disorder). Four (66.6%) of the hospitalized patients were <6 months.

Results of liver enzyme assay were available for only 23 patients, 9 of whom (39.1%) had mildly elevated aspartate aminotransferase (AST) (32.1±17.1 U/L, max.: 65 U/L) and alanine aminotransferase (ALT) (31.8±21.6, max.: 70 U/L) levels. In our laboratory, the AST reference value is <46 and the ALT reference value is <39 U/L. None of the patients developed H1N1-related complications.

All patients were given oseltamivir (2 doses at 3 mg/kg/dose for 5 days). None of the patients manifested any gastrointestinal side effects

Table I. Distribution of Demographic Characteristics and Symptoms of the Patients

Demographic characteristics	n (%)
Gender	
Male	21 (60)
Female	14 (40)
Age	
<3 months	4 (11.4)
3-5 months	13 (37.1)
6-9 months	10 (28.5)
10-12 months	8 (22.8)
Symptoms	
Fever	32 (91.4)
Nasal discharge-blockage	27 (77.1)
Cough	31 (88.5)
Breathing difficulties	14 (40)
Hospitalization rate	6 (17.1)
RT-PCR positivity	31 (88.5)

RT-PCR: Real-time reverse transcriptase polymerase chain reaction.

(vomiting, nausea, diarrhea, etc.), feeding problems, dizziness/confusion, sleepiness, change in behavior, encephalopathy, skin rashes, or any other adverse effects. Elevations in AST (33.2±15.7 U/L) and ALT (32.7±20.4 U/L) were not observed in association with oseltamivir, and the elevation rate was the same at admission and after treatment (8/23, 34.7%). Use of oseltamivir treatment did not have a statistically significant effect on liver enzymes ($p>0.05$).

Discussion

Four antiviral agents are currently approved for the treatment of influenza. The H1N1 influenza A strain responsible for the 2009 pandemic is naturally resistant to the adamantanes (M2 inhibitors): amantadine and rimantadine[7-12]. The neuraminidase inhibitors zanamivir (Relenza®) and oseltamivir (Tamiflu®) are the only available treatment options for the management of both influenza A and influenza B infections[8-11,13]. Oseltamivir (Tamiflu®) is a widely used antiviral for the treatment and prophylaxis of influenza. Prior to the pandemic, use of oseltamivir was not recommended in patients younger than one year of age. However, the severe course of infection observed in children younger than one year of age prompted the FDA to approve the use of oseltamivir in this age group, despite the potential risk of adverse effects.

In recent years, there have been case reports of neuropsychiatric events during oseltamivir treatment mainly in Japan, the United States and other countries[14]. Reported neuropsychiatric side effects include delirium, abnormal behavior, hallucinations, convulsions, and encephalitis[5,15-20]. Especially in Japan, a high rate of neurological symptoms was reported due to the influenza A infection itself, as well as in association with oseltamivir treatment. This difference may be attributed to variations in the pharmacokinetic profile and drug metabolism of the Japanese population[5,15,17-19]. Deaths due to oseltamivir have also been reported, mainly from Japan[20]. In a study by Morishima et al.[5], 148 of 202 patients (73.2%) had influenza-related encephalitis/encephalopathy. In animal studies with oseltamivir, it was observed that drug concentrations in the brains of baby rats were 1500 times higher than in the brains of adult rats, which led to restrictions in the use of this drug in young infants[21].

In another study from Japan, the frequencies of neurological symptoms before and after initiation of oseltamivir treatment were compared, and no statistically significant difference was observed[22]. Neurological symptoms reported in that study included abnormal behaviors, illusions, delusions, loss of consciousness, and phobias. The authors suggested that the development of neurological symptoms does not necessarily warrant antiviral treatment, and that initiation of treatment does not worsen the clinical picture. In contrast to the high incidence of neurological findings in Japan, none of the patients in our study developed any neurological symptoms during the course of the disease or after treatment was initiated.

Several dermatological side effects have also been reported in association with oseltamivir, ranging from localized conditions such as eczema, petechia and urticaria to more systemic involvement in the form of Steven-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis[23-25]. None of our patients developed any dermatological symptoms.

Gastrointestinal adverse effects limit the use of the drug in young children, with nausea and vomiting being a particular problem in this age group[26]. In a study of 157 infants, gastrointestinal side effects were the most frequently observed adverse effects of oseltamivir, with nausea and vomiting developing in 50% of patients[1]. Interestingly, oseltamivir was well tolerated by patients in our study, with no record of nausea and vomiting developing in any of them.

Transient elevations in liver enzymes associated with H1N1 infection have been reported in less than 3% of patients[27], and fulminant hepatitis is very rare[28]. Whitworth et al.[29] reported on four cases of acute liver failure due to influenza A infection in their group of patients ranging from 14-39 years of age. Hancerli et al.[30] showed that the rate of elevation in AST was 21% in hospitalized pediatric patients at admission. In our study, mild elevations in liver transaminases were observed in 39.1% of patients at admission and there was no progression in those for whom results of a blood work-up were available, with no case of acute liver failure.

Children under one year of age are considered a high-risk group and should be treated. The youngest patient treated with oseltamivir reported in our country (Turkey) was 28 days old[31] and in our patients, the youngest was 26 days old. Treatment should be initiated as soon as possible after the onset of symptoms, without delaying until test results are obtained[6,32]. During the pandemic, our hospital adhered to a similar protocol where treatment was offered upon suspicion of H1N1 influenza A infection. Although the greatest clinical benefit is observed when treatment is started within 48 hours after the appearance of initial symptoms, several investigators have reported lower mortality rates and shorter hospital stays even when treatment is initiated after the first 48 hours[6,32]. The mean time to presentation in our patient population was two days. However, the lack of a control group prevents us from drawing a conclusion regarding the clinical benefits of oseltamivir. The highest hospitalization rate occurred in children aged less than six months, and 83.3% of all hospitalized children had at least one underlying chronic disorder. In all 35 of our patients, oseltamivir treatment was initiated upon suspicion of H1N1 infection.

Practicing pediatricians are still confused about oseltamivir use because of the lack of clinical data, and thus our findings provide preliminary evidence in support of the use of this drug. Our study results suggest that oseltamivir is well tolerated in young infants and could be used in the treatment of influenza A in this age group. However, there is a need for more comprehensive prospective studies before a conclusion can be made regarding the efficacy and safety of this drug in young children.

REFERENCES

1. Siedler K, Skopnik H. Oseltamivir for treatment of influenza in infants less than one year: a retrospective analysis. Pediatr Infect Dis J 2010; 29: 495-498.
2. Neuzil KM, Zhu Y, Griffin MR, et al. Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study. J Infect Dis 2002; 185: 147–152.
3. Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Surveill Summ 2011; 60: 1-28.
4. Dawood FS, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009; 360: 2605-2615.
5. Morishima T, Togashi T, Yokota S, et al. Encephalitis and encephalopathy associated with an influenza epidemic in Japan. Clin Infect Dis 2002; 35: 512-517.
6. World Health Organization (WHO). WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. Geneva, Switzerland: World Health Organization; 2009. Available from: http://www.who.int/csr/resources/publications/swineflu/h1n1-use-antivirals-20090820/en/index. html
7. T.C. Sağlık Bakanlığı. Pandemik (H1N1) 2009 Gribi Klinik Vaka Yönetimi (25 Kasım 2009). Erişim adresi: http://www.grip.saglik.gov.tr
8. Jain R, Goldman RD. Novel influenza A (H1N1). Clinical presentation, diagnosis, and management. Pediatr Emerg Care 2009; 25: 791-796.
9. Centers for Disease Control and Prevention. H1N1 flu. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season. Atlanta, GA: Centers for Disease Control and Prevention; 2009. Available from: http://www.cdc.gov/h1n1flu/recommendations.htm
10. World Health Organization (WHO). WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. Geneva, Switzerland: World Health Organization; 2009. Available from: http://www.who.int/csr/resources/publications/swineflu/h1n1-use-antivirals-20090820/en/index. html
11. Sullivan SJ, Jacobson RM, Dowdle WR, Poland GA. 2009 H1N1 influenza. Mayo Clin Proc 2010; 85: 64-76.
12. Centers for Disease Control and Prevention. FluView: week ending May 20, 2010. Atlanta, GA: US Department of Health and Human Services, CDC; 2010. Available at http://www.cdc.gov/flu/weekly.
13. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM; Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Surveill Summ 2011; 60: 1-24.
14. 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: 1097-1114.
15. Sugaya N. Influenza-associated encephalopathy in Japan. Sem Pediatr Infect Dis 2002; 13: 79-84.
16. Huang Y-C, Lin TY, Wu SL, Tsao KC. Influenza A-associated central nervous system dysfunction in children presenting as transient visual hallucination. Pediatr Infect Dis J 2003; 22: 366-368.
17. Togashi T, Matsuzono Y, Narita M, Morishima T. Influenza associated acute encephalopathy in Japanese children in 1994-2002. Virus Res 2004; 103: 75-78.

18. Okumura A, Nakano T, Fukumoto Y, et al. Delirious behavior in children with influenza: its clinical feature and EEG findings. Brain Dev 2005; 27: 271-274.

19. Maricich S, Neul JL, Lotze TE, et al. Neurologic complications associated with influenza A in children during the 2003-2004 influenza season in Houston, Texas. Pediatrics 2004; 114: 626-633.

20. Okamoto S, Kamiya I, Kishida K, Shimakawa T, Fukui T, Morimoto T. Experience with oseltamivir for infants younger than 1 year old in Japan. Pediatr Infect Dis J 2005; 24: 575-576.

21. Alert letter. (US Food and Drug Administration web site). December, 2003. Available at: http://www.fda.gov/medwatch/SAFETY/2003/tamiflu-deardoc.pdf.

22. Tanabe T, Hara K, Nakajima M, Shimakawa S, Tamai H. Oseltamivir treatment for children showing abnormal behavior during influenza virus infection. Brain Dev 2010; 32: 440-444.

23. Silva ME, Cherry JD, Wilton RJ, Ghafouri NM, Bruckner DA, Miller MJ. Acute fever and petechial rash associated with influenza A virus infection. Clin Infect Dis 1999; 29: 453-454.

24. Holdiness MR. Adverse cutaneous reactions to influenza vaccinations and chemotherapy. Int J Dermatol 2001; 40: 427-430.

25. Nordstrom BL, Oh K, Sacks ST, L'Italien GJ. Skin reactions in patients with influenza treated with oseltamivir: a retrospective cohort study. Antivir Ther 2004; 9: 187-195.

26. Jamieson B, Jain R, Carleton B, Goldman RD. Use of oseltamivir in children. Can Fam Physician 2009; 55: 1199-1201.

27. Carrillo-Esper R, Pérez-Bustos E, Ornelas-Arroyo S, Albores-Saavedra J, Uribe M. Liver involvement in severe human influenza a H1N1. Ann Hepatol 2010; 9(1): 107-111.

28. Adams DH, Hubscher SG. Systemic viral infections and collateral damage in the liver. Am J Pathol 2006; 168: 1057-1059.

29. Whitworth JR, Mack CL, O'Connor JA, Narkewicz MR, Mengshol S, Sokol RJ. Acute hepatitis and liver failure associated with influenza A infection in children. J Pediatr Gastroenterol Nutr 2006; 43: 536-538.

30. Hancerli S, Somer A, Salman N, et al. Clinical and epidemiological characteristics of pandemic influenza A/(H1N1) in hospitalized pediatric patients at a University Hospital, İstanbul. J Pediatr Infect 2010; 4: 104-109.

31. Taşar MA, Arıkan Y, Arıkan Fİ, Dallar Y. Pandemic influenza in two newborns. J Pediatr Infect 2010; 4: 120-122.

32. Centers for Disease Control and Prevention (CDC). H1N1 flu. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season. Atlanta, GA: Centers for Disease Control and Prevention; 2009. Available from: http://www.cdc.gov/h1n1flu/ recommendations.htm