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Safety of Oseltamivir Compared With the Adamantanes in Children Less Than 12 Months of Age

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Abstract

Background—When oseltamivir is administered in extremely high doses (500–1000 mg/kg) to young juvenile rats, central nervous system toxicity and death occurred in some animals. Mortality was not observed in older juvenile rats, suggesting a possible relationship between neurotoxicity and an immature blood-brain barrier. To assess potential neurologic adverse effects of oseltamivir use in infants, a retrospective chart review was performed in infants less than 12 months of age who received oseltamivir, amantadine, or rimantadine.

Methods—The primary objective was to describe the frequency of neurologic adverse events among children less than 12 months of age who received oseltamivir compared with those receiving adamantanes. Medical record databases, emergency department databases, and/or pharmacy records at 15 medical centers were searched to identify patients.

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Results—Of the 180 infants identified as having received antiviral therapy, 115 (64%) received oseltamivir, 37 (20%) received amantadine, and 28 (16%) received rimantadine. The median dose of oseltamivir was 2.0 mg/kg/dose in 3- to 5-month-old and 2.2 mg/kg/dose in 9- to 12-month-old infants. The maximum dose administered was 7.0 mg/kg/dose. There were no statistically significant differences in the occurrence of adverse neurologic events during therapy among subjects treated with oseltamivir versus those treated with the adamantanes ($P=0.13$).

Conclusions—This is the largest report to date of oseltamivir use in children less than 12 months of age. Neurologic events were not more common with use of oseltamivir compared with that of the adamantanes. Dosing of oseltamivir was variable, illustrating the need for pharmacokinetic data in this younger population.

Keywords

oseltamivir; neuraminidase inhibitor; antiviral; children; infant; adamantanes; safety

Oseltamivir, an orally bioavailable neuraminidase inhibitor, is licensed in the United States for treatment and chemoprophylaxis of influenza in children ≥ 1 year of age.¹ Another neuraminidase inhibitor, zanamivir, also is licensed for use in children ≥ 7 years of age for treatment and ≥ 5 years of age for chemoprophylaxis.¹ It is delivered via an inhaler device that is difficult for younger children to use. In a prospective, randomized, blinded, placebo-controlled study in influenza-infected children 1 to 12 years of age, a 5-day treatment course of oseltamivir was associated with a median reduction in overall clinical illness of 36 hours and a reduction in fever of 25 hours.² Additionally, the incidence of acute otitis media was reduced by 44% compared with placebo recipients. A significant decrease in viral shedding was also noted in treated children, with few treated children still shedding virus on day 4 of therapy. The most common adverse drug effect was vomiting (14% of oseltamivir-treated subjects vs. 8% of placebo recipients).²

The safety of oseltamivir therapy in infants younger than 12 months of age is a potential concern. The oseltamivir package insert states that use of oseltamivir in this age group is not indicated,³ based on preclinical findings in juvenile rats.⁴ A single 1000 mg/kg dose of oseltamivir (about 250 times the recommended dose in children) in 7-day-old rats resulted in excess deaths in association with unusually high exposure to both the active metabolite of oseltamivir and the prodrug. Concentrations of the prodrug in juveniles were approximately 1500 times greater than those seen in adult animals, suggesting that these adverse outcomes may be related to an immature blood-brain barrier or to immaturity of conversion of prodrug to active metabolite in juvenile animals. While the applicability of these rat studies to human infants is questionable due to significant differences in oseltamivir metabolism between the 2 species and the extremely high doses employed in the animal trials, caution is warranted until appropriate pediatric studies can be conducted. Reassuringly, a retrospective study of infants younger than 1 year of age in Japan did not find an association between use of oseltamivir and either mortality or encephalopathy.⁵

Despite the wording of the package insert, off-label use of oseltamivir in infants less than 12 months of age occurs in the United States, particularly in infants who are seriously ill or considered to be at high risk of complications from influenza infection or in those who present with severe disease. To assess potential neurologic adverse effects of oseltamivir in infants, a retrospective chart review was performed in North America by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) of infants less than 12 months of age who received oseltamivir compared with either of the adamantanes (amantadine or rimantadine).

MATERIALS AND METHODS

Study Objectives

The primary objective of this retrospective chart review was to describe the frequency of neurologic adverse events among children less than 12 months of age who received oseltamivir, amantadine, or rimantadine for suspected or laboratory diagnosed influenza. Secondary objectives were to describe the frequency of all adverse events among these children, and to compare the frequency of adverse events at the various doses of oseltamivir, which were administered.

Study Population

A total of 15 academic medical centers participated in the study. Following institutional review board approval, medical record databases, emergency department databases, and/or pharmacy records between 2000 and 2006 at the participating centers were searched to identify male and female patients of any race or ethnicity less than 12 months of age who were treated with oseltamivir, rimantadine, or amantadine for suspected or laboratory-diagnosed influenza in the inpatient or outpatient setting. An investigator from the CASG Central Unit traveled to each site and redacted data from the records of identified children. Before beginning the study, this investigator completed a course in the protection of human subjects in research and was fully trained in medical record extraction. The frequency and type of adverse events occurring within 30 days of completion of antiviral therapy were recorded, with particular emphasis on the assessment of any neurologic condition noted in the medical records. Records also were assessed for evidence of influenza signs and symptoms. Known complications of influenza were recorded as adverse events attributable to the disease process and not likely to be attributable to treatments.

Statistical Considerations

Fisher exact tests were used to compare events related to each body system by treatment cohort. To compare subjects with neurologic events during therapy with those without such adverse events, χ^2 analyses and Kruskal-Wallis tests were used for categorical and continuous factors, respectively.

RESULTS

Study Population

A total of 180 subjects' charts from 15 centers were identified and then abstracted. The numbers of subjects enrolled per center are identified in Table, Supplemental Digital Content 1, <http://links.lww.com/INF/A231>.

Of total, 33 subjects were 0 to 2 months of age (58% oseltamivir, 18% rimantadine, 24% amantadine); 29 subjects were 3 to 5 months of age (55% oseltamivir, 24% rimantadine, 21% amantadine); 58 subjects were 6 to 8 months of age (64% oseltamivir, 19% rimantadine, 17% amantadine); and 60 subjects were 9 to 12 months of age (72% oseltamivir, 6% rimantadine, 22% amantadine). Most of subjects were treated as inpatients (97%, 90%, 86%, and 82% in each age group, respectively). Overall, 115 (64%) of the 180 subjects received oseltamivir, 28 (16%) received rimantadine, and 37 (20%) received amantadine. Of the oseltamivir recipients, 88.8% had documented influenza infection, compared with 84.4% of subjects treated with an adamantane.

Demographic and other baseline characteristics are presented in Table, Supplemental Digital Content 1, <http://links.lww.com/INF/A231>, by treatment group (oseltamivir vs. amantadine or rimantadine). The 3 factors were found to be different for subjects treated with

oseltamivir versus those treated with rimantadine or amantadine: (1) more subjects treated with oseltamivir were hospitalized ($P=0.04$); (2) all subjects treated with rimantadine or amantadine (with virus type recorded) had type A influenza ($P=0.001$); and (3) oseltamivir recipients were more likely to be full-term at birth ($P=0.04$). Of note, half of infants in each treatment group had complicated neonatal courses, with approximately 10% of those having neurologic complications.

Abnormalities During Therapy

Body system abnormalities by treatment group are listed in Table 1. There were no statistically significant differences in the numbers of neurologic abnormalities during therapy for the subjects treated with oseltamivir compared with those treated with the adamantanes ($P=0.13$). The only body system with differences by treatment group was the head/eyes/ears/nose/throat system (eg, otitis media, conjunctivitis, rhinorrhea, etc), in which subjects treated with oseltamivir were less likely to develop abnormalities during therapy compared with recipients of amantadine or rimantadine ($P<0.01$).

Neurologic Abnormalities

Specific neurologic abnormalities experienced during treatment are detailed in Table 2. All abnormalities that potentially reflected neurologic involvement were consistent with influenza disease (eg, vomiting or decreased oral intake), related to preexisting underlying neurologic conditions (eg, hypoxic ischemic encephalopathy or congenital cytomegalovirus infection), or explainable by a concomitant medication (eg, lorazepam). Two subjects had possible seizures or seizure-like movements during therapy with no preexisting history of such events, but in both cases the seizures were not thought to be related to antiviral therapy. The first subject had pertussis as well as influenza A, and experienced possible seizure movements on day 2 of amantadine therapy. The second subject had respiratory failure due to influenza A and had a first seizure 5 hours before starting oseltamivir therapy. This patient had a pneumothorax and cardiac arrest, and went on to develop hypoxic ischemic encephalopathy, ongoing seizures, hemiparesis, and motor developmental regression. A third subject had a seizure during amantadine therapy but had an earlier history of seizures.

In this retrospective review, only 33% of the subjects had Glasgow Coma Score (GCS) information available in their medical records. The end-of-treatment ranked verbal score was slightly lower for oseltamivir treated subjects ($P=0.04$); however, total scores (median = 15) were identical between the 2 therapies ($P=0.40$).

Demographic and baseline characteristics were evaluated to assess whether there were differences between subjects with neurologic events versus those without. No characteristics were statistically associated with abnormal neurologic events, including need for hospitalization, presence of a confirmed influenza diagnosis, viral type, gender, race, birth weight, neonatal medical course after birth, antiviral therapy (oseltamivir vs. adamantane), or abnormal neurologic findings by history or at baseline.

Mortality

A total of 46% of subjects returned to the institution providing medical care for influenza for subsequent medical care. One death occurred within 30 days following initiation of the influenza antiviral medications. This subject, who received oseltamivir, had a history of failure to thrive, and had preexisting interstitial lung disease. As a result of progressing lung disease during hospitalization, the family elected to withdraw life-support.

Antiviral Dosing

The median dosage of oseltamivir was 2.0 mg/kg/dose in 3-to 5-month-old infants and 2.2 mg/kg/dose in 9- to 12-month-old infants (Table 2). The maximum dose administered was 7.0 mg/kg/dose, given to a baby in the 0 to 2 month age group. Only one subject, in the 9 to 12 month age group, had vomiting associated with administration of medication. Subjects treated with oseltamivir received antiviral treatment for a median of 5.0 days (Table 3), as did subjects treated with rimantadine or amantadine ($P=0.51$).

DISCUSSION

This is the largest report to date of oseltamivir use in infants younger than 12 months of age. In our retrospective study, neurologic events were not more common during oseltamivir treatment than with either amantadine or rimantadine. A previous report of 103 Japanese infants who received oseltamivir also found no association between the use of oseltamivir and either mortality or encephalopathy.⁵ Subjects in that study had a mean age of 7.5 months, and received 4.0 mg/kg/d of oseltamivir for a mean of 3.9 days.

A complete understanding of neurotoxicity, if any, associated with oseltamivir use is important because of the juvenile rat data previously discussed,⁴ in addition to reports of rare neuropsychiatric events in adolescent patients receiving oseltamivir.^{6,7} The US Food and Drug Administration reviewed data on the latter events, and wording in the package inserts of oseltamivir, zanamivir, and the adamantanes has been modified to indicate that existing data suggest that neuropsychiatric adverse events can occur in patients with influenza infection, with or without antiviral therapy.^{3,8} These events do not appear to be associated solely with use of oseltamivir or the neuraminidase inhibitor class of antiviral medications.⁹

Oseltamivir pharmacokinetics and clinical efficacy have been studied in pediatric patients 12 months of age and older.^{2,10} Accordingly, oseltamivir is licensed for treatment and prophylaxis of influenza in children ≥ 1 year of age. The broad dosing ranges of oseltamivir used in infants younger than 12 months in the current study (1–7 mg/kg/dose) illustrate the need for pharmacokinetic data to provide dosing guidelines for this younger population. The NIAID CASG currently is conducting a prospective pharmacokinetic and safety study of oseltamivir among children less than 2 years of age, utilizing an age-deescalation trial design, which includes the neonatal age range.¹¹

Infants and young children are at greater risk of mortality from epidemic influenza than are older children.^{12–16} with the highest mortality rates occurring in those less than 2 years of age.¹² Furthermore, young age is a risk factor independent of any underlying medical problems.^{13–16} An understanding of these risks has led the Centers for Disease Control and Prevention Advisory Committee for Immunization Practices to revise recommendations for influenza vaccination to include universal vaccination of all children ≥ 6 months of age.¹⁷ Influenza immunization of younger infants is not recommended because of insufficient data. Although the finding that only one infant in the current study died as a consequence of influenza is encouraging, the retrospective nature of the trial precludes any conclusions about antiviral efficacy. The lower incidence of head/eyes/ears/nose/throat abnormalities in the oseltamivir-treated patients may reflect the known benefit of this drug in preventing otitis media during influenza infection.²

Worldwide, influenza resistance to oseltamivir developed rapidly during 2008. By the 2007 to 2008 season, 11.3% of influenza A(H1N1) isolates in the United States were resistant to oseltamivir.¹⁸ Then, with the 2008 to 2009 influenza season, oseltamivir resistance among A(H1N1) isolates skyrocketed to essentially 100% in many parts of the world, including the

United States^{19–21}; the overwhelming majority of A(H1N1) isolates remain susceptible to the adamantanes. On the other hand, the influenza A(H3N2) viruses continue to have near universal resistance to amantadine and rimantadine, but remain susceptible to oseltamivir and zanamivir. Influenza B viruses remain susceptible to oseltamivir and zanamivir as well. Knowledge of the appropriate dosing of each of these medications in infants under 12 months of age is lacking, further complicating the development of additional alternative treatment strategies for this vulnerable population.

These retrospective data provide some reassurance that neurologic events are not associated with oseltamivir administration at moderate or high frequencies in infants less than 12 months. However, rare neurologic events cannot be excluded by our analysis, because of the modest sample size of this study and the difficulty in discerning causality of observed events in retrospective trials, especially in the setting of an illness with known neurologic effects. The CASG's ongoing prospective investigation of oseltamivir pharmacokinetics and safety in young children will provide additional data to assure safe use of this medication in young infants.

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TABLE 1

No. Subjects With Abnormalities During Antiviral Therapy

Body System	Oseltamivir n = 115	Rimantadine or Amantadine n = 65	P
Neurologic	19 (16.5%)	17 (26.2%)	0.13
Pulmonary	59 (51.3%)	30 (46.2%)	0.54
Gastrointestinal	26 (22.6%)	14 (21.5%)	1.00
Cardiovascular	4 (3.5%)	4 (6.2%)	0.46
HEENT (eg, otologic, ocular, etc.)	2 (1.7%)	10 (15.4%)	<0.01
Dermatologic	5 (4.3%)	4 (6.2%)	0.72
Systemic response	6 (5.2%)	4 (6.2%)	0.75
Genitourinary	4 (3.5%)	2 (3.1%)	1.00
Musculoskeletal	2 (1.7%)	0 (0.00%)	0.54
Hematologic/lymphatic	6 (5.2%)	2 (3.1%)	0.71
Hepatobiliary/pancreatic	5 (4.3%)	0 (0.00%)	0.16
Endocrine/metabolic	0 (0.00%)	1 (1.5%)	0.36

TABLE 2

Abnormal Neurologic Events During Therapy

	Oseltamivir n = 115	Rimantadine or Amantadine n = 65
Total no. events	22	18
Agitated	1	0
Drug-induced hypotony	0	1
Hypertonia	1	0
Hyporeflexia	0	1
Hypotonia	2	1
Irritable	13	13
Left hemiparesis	1	0
Possible seizure movements	0	1
Hyporesponsive due to sedation	2	0
Seizures	1	1
Tone	1	0

TABLE 3

Oseltamivir Dosing Utilized by Participating Sites

Oseltamivir Dose	0–2 mo N = 33	3–5 mo N = 29	6–8 mo N = 58	9–12 mo N = 60
Median (mg/kg/dose)	2.08	2	2.04	2.21
Min-Max (mg/kg/dose)	(0.99, 6.99)	(0.84, 6.38)	(1.53, 4.28)	(1.74, 4.96)
N	19	15	33	38
Median (mg/dose)	10	12.5	15	20
Min-Max (mg/dose)	(4, 30)	(3, 30)	(7, 30)	(9, 40)
N	19	16	37	41
Median duration of therapy (d)	5.0	6.0	5.0	5.5