

Early Oseltamivir Treatment of Influenza in Children 1-3 Years of Age: A Randomized Controlled Trial

BACKGROUND

- At the time of the study, oseltamivir was the only recommended drug for treating influenza in children <5 years of age.
- A previous study showed oseltamivir to reduce duration of illness and incidence of acute otitis media (AOM) when started within 48 hours of the onset of symptoms.
- Investigators hypothesized that effectiveness of the drug could be increased if started earlier than within 48 hours of the appearance of symptoms.

OBJECTIVE

- To assess the efficacy of early oseltamivir treatment (started within 24 hours of the onset of influenza symptoms) in preventing the development of acute otitis media as a complication of influenza in children aged 1-3 years.

METHODS

- **Design:** Single site, randomized, double-blind, placebo-controlled, investigator- initiated trial
- **Inclusion Criteria:**
 - Age 1-3 years
 - Fever for ≤ 24 hours
 - Fever ≥ 38.0 C and at least one respiratory symptom OR fever ≥ 38.0 C and a positive influenza rapid test
- **Exclusion Criteria:**
 - Confirmed infection with any other respiratory virus than influenza.
 - Suspicion of invasive bacterial infection requiring immediate admission to hospital
 - Evidence of a poorly controlled underlying medical condition
 - Known immunosuppression (malignancy, transplant, drugs)
 - Known allergy to oseltamivir or acetaminophen
 - Received oseltamivir within 4 weeks
 - Participation in another clinical trial with an investigational drug
- **Primary Outcome Measure:**
 - Development of acute otitis media in children with laboratory-confirmed influenza in whom the treatment was started within 24 hours of the onset of symptoms
- **Secondary Outcome Measures:**
 - Time to resolution of illness, time to resolution of all symptoms, time to resolution of fever, days of parental absence from work, days of child's absence from day care, use of relief medications or antibiotics, incidence of complications other than acute otitis media, and hospitalization
- **Treatments:**
 - 203 patients received oseltamivir and 205 received placebo
 - After confirmation of influenza:
 - 37 patients with received oseltamivir 30 mg twice daily for children weighing <15.0 kg or 45 mg twice daily for children weighing 15.1–23.0 kg.
 - 61 patients with influenza received placebo twice daily
 - Children received clinical examinations, and parents filled out detailed symptom diaries for 21 days
- With a 5% level of significance and 80% power, the number of influenza-infected children needed in each group was 77. Neither group met this number.
- Intention-to-treat data handling was used for safety analyses. Efficacy analysis was performed on only those patients who had laboratory-confirmed influenza.

RESULTS

- A total of 408 patients (203 in the oseltamivir group and 205 in the placebo group) received treatment. Of those, 98 patients had confirmed influenza (37 in the treatment group and 61 in the placebo group). In patients with confirmed influenza, 79 had Influenza A, and 19 had Influenza B.
- **Primary Outcome Measure:** When started within 12 hours of the onset of symptoms, oseltamivir statistically significantly decreased the relative risk incidence of acute otitis media by 85% ($p=0.02$, 95% CI - 25%-97%). No statistically significant decrease in incidence was seen when treatment was started within 24 hours.
- **Secondary Outcome Measures:** Oseltamivir statistically significantly decreased the time to resolution of illness, time to resolution of fever, time to resolution of all symptoms, number of parental days absent from work, number of child's days absent from day care, and number of doses of relief medication administered in 'Any influenza' groups and the Influenza A groups. No statistically significant benefit was seen on Influenza B.
- **Authors' conclusion:** Oseltamivir treatment started within 24 hours of symptom onset provides substantial benefits to children with influenza A infection.

STRENGTHS

- Randomized, controlled trial
- Very low dropout rate
- Inclusion/exclusion criteria was appropriate and representative
- Clinically significant outcome measures

LIMITATIONS

- Inadequately powered
- Small sample size
- Mailed announcements and local advertisements were used for recruitment.
- Clinic hours could have affected ability to obtain oseltamivir within 12/24 hours.
- Relief medication use allowed and monitored but not accounted for. Its use could have influenced symptoms.
- Adherence was self-reported and not verified.
- Study was performed over two flu seasons; possible variability in virus strains exists.
- Influenza vaccination recommendations changed during the study.

CONCLUSION

- Despite the fact that oseltamivir only statistically significantly decreased the incidence of AOM when taken within 12 hours of appearance of symptoms, I feel there is a place for oseltamivir in therapy. Even when taken within 24 hours of appearance of symptoms, it has clinically beneficial effects on a number of secondary outcomes.
- Annual influenza vaccinations should still be recommended in pediatric patients, but in patients in whom the vaccination fails or who do not receive the vaccination, oseltamivir would be a useful alternative.
- It could be logistically difficult, however, for parents of potential patients to get the child to the doctor and to obtain the medicine in the allotted time to see optimal clinical benefit.
- Further studies directly comparing treatments started within 24 and 48 hours are needed. Additionally, treatment comparing oseltamivir versus peramivir, the newest neuramidase inhibitor, may be warranted.

REFERENCE:

Heinonen S, Silvennoinen H, Lehtinen P, Vainionpää R, Vahlberg T, Ziegler T, Ikonen N, Puhakka T, Heikkinen T. Early oseltamivir treatment of influenza in children 1-3 years of age: a randomized controlled trial. Clin Infect Dis. 2010. Oct 15;51(8):887-94.

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