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Fact Sheet

Use of Oseltamivir in Children and Adolescents

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Facts

1. Oseltamivir (Tamiflu) is a neuraminidase inhibitor licensed for the treatment of uncomplicated acute illness due to influenza (A or B) infection in patients 1 year and older who have been symptomatic for no more than 48 hours.

2. One double-blind placebo-controlled treatment trial conducted in influenza-infected (67% influenza A, 33% influenza B) patients 1 to 12 years (median 5 years), Tamiflu of 2 mg/kg twice daily for 5 days, started within 48 hours of symptoms onset, significantly reduced the overall clinical illness by 36 hours and a reduction of fever by 25 hours compared to placebo.

3. There is a publication (sponsored by Roche) on the effect of oseltamivir reducing the risk of pneumonia in children with "clinical influenza" but without virologic diagnosis of influenza (Curr Med Res Opin 2007;23: 523-31) and another one on the reduction of influenza-related complications (pneumonia, otits media), hospitalization and healthcare expenditure with oseltamivir treatment, also sponsored by Roche (Expert Opinion 2008;9:151-61).

4. According to Roche
   - the efficacy of Tamiflu in the treatment of patients with chronic respiratory and cardiac disease has not been established.
   - the efficacy of Tamiflu in the treatment and prophylaxis in immunocompromised patients has not been established.
   - the safety and efficacy in the repeated use of Tamiflu in treatment and prophylaxis have not been established.

5. Tamiflu is not licensed for use in infants below 12 months of age because of concern of increased risk of neurotoxicity of the drug based on animal studies.

6. Adverse events
   - Most common are gastrointestinal disturbances: vomiting in 14% of oseltamivir-treated compared with 8% in placebo-treated children.
   - Neuropsychiatric events
     From the approval date of oseltamivir in 1995 to 31 May 2007, 596 neuropsychiatric adverse events were reported.

     http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4325s2_02_Tamiflu,%20Rothstein,%20PharmD%20(FDA).pdf

     http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4325b_02_01_Tamiflu%20Background_Summary.pdf

     - 61% were paediatric patients (≤21 years)
     - 75% were from Japan
     - 5 with fatal outcome, also reports of delirium with impulsive behaviour, self-injury and violent behaviour
     - these neuropsychiatric cases appear to be temporally related to oseltamivir use
       - median onset of 24 hours, after a median of 1-2 doses.
       - some developed symptoms within half an hour.
     - rapid (median of 6 hours) and full recovery from the adverse event once oseltamivir was discontinued.

7. It is unclear whether these neuropsychiatric events are drug-related, disease manifestation or a combination. Since the incidences of influenza-related neurologic events (febrile seizures and encephalitis) in Chinese children are more similar to that of the Japanese than Caucasians, particular consideration should be given to this adverse event before prescribing oseltamivir.

8. A recent study from Beijing showed that a SNP in the human cytosolic sialidase gene (R41Q of HsNEU2) could be a potential link with adverse neuropsychiatric reaction to oseltamir; this SNP is present in 9.29% of Asian population and none of the European and Africa American population (Cell Res 2007;17:357).

9. The Ministry of Health, Labour and Welfare of Japan recommended (March 2007) that oseltamivir should not be used to treat teenagers between 10-19 years of age with influenza because of increased neuropsychiatric side effects of oseltamivir in this group of patients. Korea has adopted a similar recommendation.

10. US FDA issued a safety alert on March 4, 2008 that the product label for Tamiflu has been revised. FDA advises practitioners to closely monitor patients taking Tamiflu for signs of abnormal behaviour. If neuropyschiatric symptoms occur, the risk and benefits of continuing treatment should be promptly evaluated.

Recommendations

- The use of oseltamivir can be considered in the treatment of children with virologically proven influenza A and B infection within 48 hours of onset of symptoms especially in patients with chronic cardiorespiratory, renal or metabolic disorders or those who are immunocompromised.
- All patients treated with oseltamivir should be closely monitored for abnormal behaviour, and when appropriate, protected against self-harm.
- Infants under 12 months or teenagers between 10 – 19 years of age should not be treated. In exceptional cases like those severely affected, treatment should preferably be prescribed after informed consent and thorough discussion of the risks and benefits of treatment with the parent:

Dosage

- <12 months 2 mg/kg twice daily for 5 days (off label use under specialist advice after informed consent)
- 1 – 9 years Recommended dose for 5 days
  - ≤15 kg 30 mg twice daily
  - 15 – 23 kg 45 mg twice daily
  - 23 – 40 kg 60 mg twice daily
  - >40 kg 75 mg twice daily
- 10 – 19 years
  - 23 – 40 kg 60 mg twice daily
  - >40 kg 75 mg twice daily

  (under specialist advice after informed consent)

Administration

- capsule 75 mg
- oral suspension 12 mg/ml
- dispensing syringe calibrated with graduations of 30, 45 and 60 mg
- 75 mg may be dispensed using 30 + 45 mg combination if patient cannot tolerate 75 mg capsule

Oseltamivir Resistance

- In previous years, studies of seasonal influenza isolates collected before oseltamivir treatment have rarely shown naturally occurring resistance to oseltamivir (J Med Virol 2007;79:1577).
- 5.5% and 18% of oseltamivir treated children in US and Japan developed in vitro resistance in influenza isolates cultured during therapy (J Pediatr Inf Dis 2001;20:127).
- The European Centre for Disease Prevention and Control reported high natural resistance to oseltamivir in an influenza A (H1N1) virus (antigenically similar to the A/Solomon Islands/3/2006 virus) circulating in Europe during the winter of 2007 – 2008 (68% Norway, 38% France, 14% Europe) [Euro Surveill 2008;13(5)].
- The US Center of Disease Control and Public Health Agency of Canada reported oseltamivir resistance in 5% and 10% of the H1N1 virus isolates respectively during this influenza season.
- No oseltamivir resistance in influenza isolates have been documented in Hong Kong up till the end of 2007. In 2008 nearly 10% of H1N1 Brisbane 59 like virus isolated (nearly 500 specimen) in the current influenza season were resistant to oseltamivir (Public Health Laboratory Centre, CHP).