World Health Organization

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ADVICE ON USE OF OSELTAMIVIR

Oseltamivir (Tamiflu®) is recommended for use for both treatment and prophylaxis of influenza. The currently recommended doses are:

For treatment of influenza

- Adults: 75 milligrams (mg) two times a day for five days.
- Children 1 year of age or older: weight adjusted doses
  - 30mg twice daily for ≤ 15 kg
  - 45mg twice daily for >15 to 23 kg
  - 60mg twice daily for >23 to 40kg
  - 75mg twice daily for >40kg
- Children up to 1 year of age: not recommended

For prevention of influenza:

- Adults and teenagers 13 years of age or older: 75 mg once a day for at least seven days.
- Children from 1 year to 13 years of age:
  - 30mg daily for ≤ 15 kg
  - 45mg daily for >15 to 23 kg
  - 60mg daily for >23 to 40kg
  - 75mg daily for >40kg

In the context of the human cases of avian influenza, WHO has reviewed the limited available information and evidence about the effectiveness and safety of oseltamivir for the treatment of patients with avian influenza and also its use as prophylaxis in health workers and those involved in managing an outbreak.

TREATMENT

The evidence for effectiveness of oseltamivir in human H5N1 disease is based on virological data from in vitro, animal models, and limited human studies and extrapolation from the results of trials in patients with ordinary human influenza. There is no direct clinical trial evidence that shows that oseltamivir is effective in human H5N1 disease because such studies have not yet been conducted. Without such trials, the optimal dose and duration of oseltamivir treatment is uncertain in H5N1 disease and therefore doses of oseltamivir used for seasonal human influenza continue to be recommended. The clinical course, and, presumably, some aspects of the immunopathogenesis, of human H5N1 disease (in particular the severe form) may be different from normal seasonal influenza requiring a different dosing approach.

At present, there is no clear evidence that shows that higher dosages than the approved ones will be more effective for patients with H5N1. However, because the optimal dosage has not been resolved by clinical trials, and because H5N1 infections continue to have a high mortality rate, prospective studies are needed urgently to determine optimal dosing and duration of treatment for H5N1. It is possible that severely ill patients might benefit from longer duration of therapy (e.g. 7-10 days) or perhaps higher doses (e.g. 300mg/day), but prospective studies are required.

In terms of safety and adverse effects, evidence from the trials in ordinary influenza shows that although oseltamivir is generally well tolerated, gastrointestinal side effects in particular may increase with increasing doses, particularly above 300mg/day.

There are no adequate data on the use of oseltamivir in pregnant women. The animal toxicology studies do not indicate direct or indirect harmful effects with respect to pregnancy or fetal development. Decisions to use oseltamivir in pregnant women should be made on a case by case basis where the potential benefit to the mother justifies the potential risk to the fetus.

WHO will continue to monitor the situation and will provide updates on the availability of clinically important new information related to the optimal dosing and duration of treatment with oseltamivir for H5N1-infected persons.

PROPHYLAXIS

The evidence for effectiveness of oseltamivir for prophylaxis of H5N1 disease is based on the results of trials of preventing ordinary influenza in healthy and elderly patients and children.

For prevention of disease in household contacts of a case of H5N1 influenza, the current recommendation is to provide adults with 75mg/day for 7-10 days from the last day of a potentially infective exposure. Children should be provided oseltamivir as prophylaxis for the same length of time with the weight-adjusted doses recommended for prevention of seasonal influenza. For people with repeated or prolonged exposure such as health care workers or personnel involved in bird culls, pre-exposure courses, repeat post-exposure courses or continuous treatment may be necessary. Continuous treatment for up to 6 weeks with 75mg/day is generally well-tolerated. The efficacy and safety of post-exposure prophylaxis have been shown in children aged 1 year and older.

Currently there is no evidence that supports an increase in prophylactic dose or duration of use for people with a single exposure to H5N1. If the contact already has fever or other symptoms suggestive of H5N1 infection, full therapeutic doses should be administered.

At this time there is little information available about a number of important aspects that may influence decisions to provide prophylaxis and to alter the dose of oseltamivir in people who become ill while taking the medicine prophylactically. Should a person develop a

febrile respiratory illness while on prophylaxis, whenever possible, they should have samples collected for viral diagnosis, and a concurrent blood sample taken for later measurement of drug concentration.

In order to evaluate the efficacy of prophylaxis, persons placed on prophylactic courses should be followed in well-designed studies that include control groups to ascertain the effectiveness of current dosing for prophylaxis.

To accumulate important additional safety information about the use of oseltamivir, it is important that all persons who are receiving it for prophylaxis are monitored for side effects. Suspected adverse events should be reported to the manufacturer and to the adverse drug reaction monitoring centre of the country.

This advice will be reviewed regularly and updated as information becomes available. It is issued without any warranty of any kind either express or implied. In no event shall WHO be liable for damages of any nature, arising out of the use of this advice.

REFERENCES:

Avian influenza A (H5N1) Infection in humans. *New Eng J Med* 2005;353:1374-85.

Tamiflu® FDA approved label, at:
http://www.fda.gov/cder/foi/label/2005/021246s017_021087s030lbl.pdf