Title | Fact sheet on antiviral therapy against influenza
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**Scope** | This fact sheet serves as a reference material for the frontline clinical staff on the antiviral agents against influenza, and principles of antiviral treatment and prophylaxis.

| Important Note: antiviral drugs for influenza are adjunct to influenza vaccine for controlling and preventing influenza, and are not substitute for vaccination |

I. **Neuraminidase inhibitors**

A. **Introduction**

1. They block cleavage of budded viruses from infected cells, promote virus aggregation and hence reduce viral release and spread.
2. They are active against both influenza A and B, including the 2009 pandemic H1N1 virus.
3. Two commonly used neuraminidase inhibitors are zanamivir (Relenza) and oseltamivir (Tamiflu).
4. There are two parenteral neuraminidase inhibitors i.e. peramivir and zanamivir. Department of Health (DH) has approved peramivir as “Emergency Stock” which requires retrospective report to DH about the names who have been given the drug according to legal requirement. Intravenous preparation of zanamivir is not available commercially and is used only in the setting of clinical trial or on compassionate ground.

B. **Clinical use of neuraminidase inhibitors**

1. Oseltamivir and zanamivir are both approved for treatment and chemoprophylaxis of influenza.
2. People who are at risk of or presented with serious influenza related complications should be given priority for use of neuraminidase inhibitors

C. **Regimen and adverse events**

**Oseltamivir**

1. For adult and children $\geq 13$ year old:
   a. Normal dosage is 75mg BD for 5 days.
   b. Dosage adjustment is required in patients with renal impairment or undergoing dialysis.
Dosing recommendations have been proposed for patients with creatinine clearance < 10 ml/min or undergoing routine renal dialysis treatment, but are based on limited pharmacokinetic data.

Table 1. Dosage adjustment of oseltamivir for renal failure

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Patients undergoing dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 - 90</td>
<td>10 - 50</td>
</tr>
<tr>
<td>75mg BD</td>
<td>30 – 50: 75mg BD</td>
</tr>
<tr>
<td></td>
<td>&lt; 30: 75mg daily</td>
</tr>
<tr>
<td></td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td>CAPD: 30mg weekly</td>
</tr>
<tr>
<td></td>
<td>HD: 30mg on non-HD day</td>
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<tr>
<td></td>
<td>CRRT: 75mg BD</td>
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</tbody>
</table>

CAPD: continuous ambulatory peritoneal dialysis; CRRT: continuous renal replacement therapy; CrCl: creatinine clearance; HD: haemodialysis

2. Dosage for children aged 1-12 year old:
   - ≤15 kg  30mg BD x 5 days
   - >15 - 23 kg  45mg BD x 5 days
   - >23 - 40kg  60mg BD x 5 days
   - >40 kg  75mg BD x 5 days

3. Oseltamivir is not currently FDA approved for use in children aged <1 year. CDC recommends that clinicians who treat children aged 3 - 11 months with oseltamivir to administer the drug at a dose of 3 mg/kg BD.

4. Serious or life-threatening adverse effects associated with oseltamivir treatment were rare (<1%). However, gastrointestinal side effects including nausea and vomiting are common. These side effects are transient and usually resolve spontaneously within one to two days; and might be less severe when the drug is taken with food.

5. Minor neurological side effects like headache, insomnia or vertigo have been associated with treatment and prophylaxis of oseltamivir.

6. A number of unusual neurologic or psychiatric events such as delirium, hallucinations, confusion, abnormal behavior, convulsions, and encephalopathy, were identified to be associated with the use of oseltamivir in children 16 years of age or younger. These events were reported almost entirely in children from Japan who received oseltamivir according to Japanese treatment guidelines.

**Zanamivir**

1. Zanamivir is taken by using an oral inhaler (Diskhaler®).
2. For treatment in adult and children ≥ 7 year old:
   - Normal dosage is 10mg (2 inhalations) BD for 5 days
   - No dose adjustment for patients with mild to moderate or severe renal impairment.
3. Use of Zanamivir diskhaler requires coordination and is potentially problematic in the very young and elderly.
4. Serious and life-threatening adverse effects associated with zanamivir treatment were uncommon (<1.5%). It may rarely cause bronchospasm in patients with asthma and bronchodilators must be readily available when it is used on such patients. In patients on inhaled bronchodilators, use it before the dose of zanamivir. It is also associated with gastrointestinal side effects like nausea (3%), diarrhea (adults 3%, children 2%) and vomiting (adults 1%, children 2%); neurological side effects including headache (2%) & dizziness (2%); and respiratory side effects like sinusitis (3%), bronchitis (2%) and cough (2%).

II. M2 inhibitors : adamantanes

A. Introduction
1. Amantadine and Rimantadine are inhibitors of influenza A virus M2 protein. They inhibit virus uncoating and thereby virus replication, and result in decreased viral shedding.
2. Rimantadine is 4-10 times more active than amantadine and has less CNS toxicity.
3. Rimantadine is not registered in Hong Kong.

B. Clinical use of amantadine for influenza
1. Amantadine is approved for treatment and chemoprophylaxis of influenza A virus infection in adults and children ≥ 1 year old.
2. Recommended treatment regimens.
   - For adults: 100mg BD po; discontinue as soon as possible based on clinical response (generally within 3-5 days or within 24-48 hours after symptoms disappear).
   - For paediatric patients
     i. 1-9 years: 5 mg/kg/day in 2 divided doses (manufacturers range: 4.4-8.8 mg/kg/day); maximum dose: 150 mg/day
     ii. ≥10 years and <40 kg: 5 mg/kg/day; maximum dose: 150 mg/day
     iii. ≥10 years and ≥40 kg: Refer to adult dosing
   - As amantadine is excreted unchanged in urine, dose need to be reduced to 100mg/day.
for elderly ≥ 65 or individuals with creatinine clearance ≤ 50ml/min. No dose adjustment is needed in hepatic dysfunction. Increase incidence of seizure in epileptic patients is noticed and warrants close monitoring if amantadine is to be used.

3. Amantadine is teratogenic and embryo-toxic in animals. Safety of M2 inhibitors in human pregnancy remains unclear.

C. Side effects

1. Side effects of amantadine
   a. Neurological: insomnia, lightheadedness, headache, hallucination, confusion, dizziness, fall.
   b. Confusion and other neurological symptoms are observed in 30% of elderly.
   c. Gastrointestinal: nausea and vomiting

2. Rimantadine is much less frequently associated with neurological side effects but GI side effects occur at similar rate compared to amantadine if creatinine clearance falls < 30ml/min.

D. Limitation in clinical use of M2 inhibitors

1. Inactivity against influenza B
2. Inactive against 2009 pandemic H1N1 virus
3. Rapid onset of resistance: resistance to adamantanes among influenza A(H3N2) isolates approach 100% for most parts of the world.
4. Adverse neurological and gastrointestinal side effects

With the availability of neuraminidase inhibitors, adamantanes are generally not indicated as the first-line antiviral therapy against influenza.

III. Treatment and prophylaxis against seasonal influenza

A. Treatment

1. General consideration:
   - Clinical judgment, based on the patient's disease severity and progression, presence of risk factors for complications of influenza, time since onset of symptoms, and likelihood of influenza, is important to consider when making decisions on antiviral treatment.
   - Early antiviral treatment may reduce the risk of complications and improve clinical outcomes of influenza (e.g., pneumonia, respiratory failure, and death). Antiviral treatment is
recommended as early as possible for any patient with confirmed or suspected influenza who
● has severe, complicated, or progressive illness; or
● is at higher risk for influenza complications.

● The greatest benefit is when antiviral treatment is started within 48 hours of influenza illness onset. Antiviral treatment may still be beneficial in patients with severe, complicated, or progressive illness, when administered more than 48 hours from illness onset.

2. Risk factors for complications of influenza:
● Children younger than 2 years old
● Adults 65 years and older;
● Persons with significant comorbid conditions:
  ■ chronic pulmonary (including asthma),
  ■ cardiovascular (except hypertension),
  ■ renal,
  ■ hepatic,
  ■ hematological (including sickle cell disease),
  ■ neurological and neurodevelopmental conditions,
  ■ metabolic disorders (including diabetes mellitus);
● Persons with immunosuppression, including that caused by medications or by HIV infection;
● Women who are pregnant or post-partum (within two weeks after delivery);
● Persons younger than 19 years of age who are receiving long-term aspirin therapy;
● Persons who are morbidly obese (body-mass index ≥40);
● Residents of nursing homes and other chronic-care facilities.

3. Oseltamivir and zanamivir are drugs of choice when antiviral treatment for influenza is indicated. Regimens are listed under points I.C.

4. For cases with severe infection due to 2009 pandemic H1N1 virus, WHO recommends that more than 5 days of treatment are likely to be required and that treatment should be continued for at least 10 days, unless there are clinical or virological data to indicate that virus replication is no longer occurring. There are safety data to support higher doses of oseltamivir; in adults, doses of up to 150 mg twice daily had been used. Caution should be exercised when considering higher doses in patients with renal impairment, for whom dose adjustment may be required.

B. Post-exposure Prophylaxis
Neuraminidase inhibitors are also effective for post-exposure prophylaxis. In the event of institutional outbreak especially in elderly homes, post exposure prophylaxis with oseltamivir 75mg daily or zanamivir 10mg daily (in individuals ≥ 5 year old) for 10 days may be indicated for persons who live or work in institutions caring for people at high risk of complication. Risk of emergence of drug-resistant viruses has been described elsewhere.

C. Use of intravenous neuraminidase inhibitors

D. Treatment and prophylaxis with neuraminidase inhibitor for novel influenza, including avian influenza A/H5N1

IV. Key references

