Issues in pharmacotherapy of 2009 H1N1 infection

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Anti-influenza therapy

- Adamantanes
  - Amantadine
  - Rimantadine

- Neuraminidase inhibitors
  - Oseltamivir
  - Zanamivir

Oseltamivir & Zanamivir

- O. Phosphate (prodrug) → O. Carboxylate (Active)
- Zanamivir (Active)

- MOA
  - Inhibits Neuraminidase enzyme
  - Inhibits all 9 NA subtypes
  - Oseltamivir: IC$_{50}$ 1.9 to 69.2 nanomolar
  - Zanamivir: IC$_{50}$ 2.2 to 30.1 nanomolar

Search for still lower IC$_{50}$ ongoing

Future NAIs in pipeline

- Peramivir (phase III)
- Laninamivir (pre-clinical)
- A-315675 (pre-clinical)

Symptom management....

Which antipyretic?

- No aspirin for children and adolescents (<18 years): risk of Reye's syndrome
- Paracetamol is DOC
Antiviral therapy…When?

- Hospitalization or antiviral therapy is not required for most patients
- Clinicians/care-givers should take into account:
  - Signs of clinical deterioration
  - Underlying conditions: chronic cardiovascular, pulmonary, diabetes, immunodeficiency
- Young children, elderly and pregnant women warrant close observation and early antiviral treatment

Which Antiviral for 2009 H1N1?

The 2009 H1N1 virus is currently

- Susceptible to - NAIs (oseltamivir and zanamivir)
- Resistant to - M2-inhibitors (amantadine and rimantadine)

How efficacious are NAIs?

- NAIs might reduce severity and duration and might contribute to prevent progression of severe disease and death due to 2009 H1N1 (based on seasonal influenza and H5N1 influenza studies)
- Results from large, adequately powered, well designed clinical trials for 2009 H1N1 still awaited

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<thead>
<tr>
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<th>Oseltamivir</th>
<th>Zanamivir</th>
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<tbody>
<tr>
<td>Formulation</td>
<td>Capsules or oral suspension</td>
<td>Powder in 5-mg blister on Rotadisk; requires Diskhaler inhalation device</td>
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<tr>
<td>Adverse effects</td>
<td>Nausea, vomiting, Abdominal pain (10-15%)</td>
<td>Bronchospasm in patients with underlying airway diseases</td>
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<td>Dose adjustments</td>
<td>Required in patients with creatinine clearance &lt; 30 ml/min</td>
<td>Not required</td>
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Adverse effect profile of NAIs

Oseltamivir

- Headache, nausea, vomiting, insomnia, vertigo, pyrexia, rash, toxic epidermal necrolysis, confusion, arrhythmia, unstable angina, seizure, aggravation of DM, hepatitis, pseudomembranous colitis

Zanamivir

- Wheezing and bronchospasm
- Not recommended for treatment of patients with underlying airway disease

Neuropsychiatric events particularly in the paediatric age group reported

What is the AE profile in Indians?

- No data of AE of NAIs in 2009 H1N1 Indian patients
- Proactive pharmacovigilance: an urgent need
  - Cohort event monitoring
  - Registry and prescription analysis—telephonic follow up of patients
    - Resource intensive
    - Higher data quality than spontaneous reports
Will restricted use of NAIs reduce resistance?

- Unrestricted availability
  - Emergence of resistance ??
    - Japan: NAIs widely used — resistance 3%
    - Norway: NAIs rarely used — resistance 67%

- Highly restricted use: Not feasible
  - Increasing incidence
  - Widespread demand

Are concomitant antibiotics required ??

In USA, the evidence suggests NOT NEEDED

Affordability issue

- Indian version is 1/3rd costly than US

BUT