Update

Role of antivirals in influenza

Influenza is a common, highly contagious and debilitating disease associated with a high incidence of complications and mortality.[1] Given its efficaceous nature and good tolerability, vaccination is the cornerstone of prevention of the disease, particularly for patients at risk, e.g. the elderly and those suffering from co-morbid conditions. However, the efficacy of this strategy can be variable and non-immunised populations remain vulnerable to influenza. Furthermore, vaccines may be poorly matched with circulating virus strains and it is not a useful intervention following infection.

M2 blockers

The administration of antiviral agents is a rational treatment option for influenza and may also complement vaccination. Some four decades ago the M2 blocker, amantadine (1-adamantanamine hydrochloride), was introduced to the market. This drug and its congener, rimantadine (not available in South Africa), specifically inhibit the replication of influenza A viruses (they are ineffective against influenza B viruses) in low concentrations of about 0.03 - 1.0 µg/ml.[2]

Amantadine

Mechanisms of action

Amantadine inhibits an early step in the viral replication process, probably viral uncoating, and also has an effect on one of the final steps of viral assembly in some strains. The drug acts on the M2 protein, a membrane protein that functions as an ion channel of the influenza A virus. By blocking the action of this protein, amantadine inhibits the acid-mediated dissociation of the ribonucleoprotein complex at an early stage of the replication process. It also potentiates acidic pH-induced conformational changes in the haemagglutinin during its transport in the cell in the later stages of replication.

Resistance

While primary resistance to amantadine is uncommon (< 1 - 2.5%) it has been found to be present in some viral isolates from avian, including H5N1, and swine origins. Resistance, associated with single nucleotide substitutions in the transmembrane region of M2, increases readily during treatment with the drug.[3] This has limited its antiviral efficacy.

Pharmacokinetics

Amantadine is well absorbed after oral administration and has a very large volume of distribution.[2] It is found in both nasal secretions and saliva in similar concentrations to that of serum. Amantadine has a plasma half-life of ± 12 - 18 hours and is excreted almost completely unchanged in the urine.

Side-effects

Side-effects observed with amantadine are minor dose-related gastrointestinal and CNS complaints. These include loss of appetite or nausea, nervousness, lightheadedness, loss of concentration and insomnia.[2]

Therapeutic uses

While amantadine has been primarily used prophylactically in epidemics in non-vaccinated patients who are at high risk of developing influenza-related complications, the rapid emergence of resistance has limited its efficacy. When used prophylactically the drug is administered in doses of 200 mg/day in divided doses to children and adults 10 - 65 years, and in doses of 100 mg/day to children 5 - 9 years and to adults over 65 years. Amantadine may also be used therapeutically in uncomplicated acute influenza A infections in the same doses as above. Treatment must be initiated within 48 hours of onset of symptoms and continued for 4 - 5 days.

Neuraminidase inhibitors

Currently, an alternative class of antiviral agents is available, i.e. the neuraminidase inhibitors (NIs). Neuraminidases, enzymes that are essential for viral replication, are present on all influenza subtypes. Numerous clinical studies have shown that when NIs are administered within 48 hours of the onset of symptoms, these agents significantly reduce illness duration, symptom onset and complications, e.g. pneumonia, bronchitis and otitis media. When NIs are used for prophylaxis, they are very effective in limiting the spread of infection in families and care facilities. For both indications outlined above, NIs are generally well tolerated, without major adverse effects. Two NIs, oseltamivir and zanamivir, are currently available in South Africa.

Oseltamivir

Oseltamivir carboxylate is a widely used NI and is indicated for the treatment and prophylaxis of influenza infections in adults and children ≥ 1 year.[4,5] It is a transition-state analogue of sialic acid that potently inhibits the neuraminidase enzymes of both influenza A and B viruses.

Mechanisms of action

Terminal sialic acid residues are cleaved by viral neuraminidases, thereby inactivating receptors that are recognised by viral haemagglutinin. These receptors are present on cell surfaces, in progeny virions and in respiratory secretions.[6] The inactivation of the cellular receptors is mandatory for viral release from infected cells. Binding of oseltamivir phosphate to these neuraminidases inhibits their activity.

Resistance

Resistance to the drug is due to mutations of the viral haemagglutinin and/or neuraminidase.

Pharmacokinetics

The phosphate salt of oseltamivir, a prodrug, is rapidly absorbed in the gastrointestinal tract. Hepatic and/or intestinal esterases convert the phosphate to the active carboxylate form of drug, ≥ 75% of the latter reaching the systemic circulation. Plasma concentrations of the active form are dose dependent, and are in excess of the levels required for inhibition of viral replication when administered at recommended dosages. Distribution of oseltamivir carboxylate in the body is wide

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and it reaches all sites where the influenza virus spreads, notably the upper and lower respiratory tract. The plasma half-life of oseltamivir is ± 6 -10 hours and unchanged drug (± 95%) is excreted into the urine.

Side-effects

Oseltamivir is well tolerated with few patients reporting transient, mostly mild, nausea and/or vomiting.[7,8] More rare side-effects include headache, fatigue, insomnia and dizziness. Resistance to the drug is low, with an overall incidence of resistant virus of 0.4% in adults and 4% in children between the ages of 1 and 12 years. However, since the emergence of resistance to NIs may increase with more widespread usage, it is important to continue monitoring the situation.

Therapeutic uses

For prophylaxis of influenza A and B oseltamivir may be administered to adults and adolescents ≥ 13 years of age. The recommended prophylactic dosage for these patients is 75 mg once daily. The drug is effective for the treatment of influenza A and B infections in adults and children ≥ 1 year of age. For adults and adolescents ≥ 13 years of age, 75 mg is administered twice daily for 5 days beginning within the first two days of onset of symptoms. For children these dosages must be weight-adjusted according to the dosage schedule printed on the package insert.

Zanamivir

This drug, similar to oseltamivir, is also a sialic acid analogue that inhibits the neuraminidases of influenza A and B viruses.

Mechanisms of action

Zanamivir has a similar mode of action to oseltamivir.[6]

Resistance

Resistance develops to zanamivir in the same way as that to oseltamivir.

Pharmacokinetics

The oral bioavailibility of zanamivir is low (< 5%) and the drug is administered by inhalation, using the diskhaler that is provided.

Side-effects

Inhaled zanamivir is generally well tolerated by adults and children. Because wheezing and bronchospasm have been reported in some patients with influenza, extreme care must be exercised when the drug is recommended for use in patients with underlying airway disease, e.g. asthma or chronic obstructive airway disease.

Therapeutic uses

Zanamivir is registered in South Africa for the treatment of influenza A and B virus infections in adults and children over 12 years.

Conclusions

While increasing resistance to amantadine is decreasing its efficacy, and because it is inactive against influenza B viruses, its use has become limited. For this reason there is growing reliance on the NIs for treatment and prophylaxis, particularly of influenza A and B infections.[9] Of the NIs, oseltamivir is currently the most widely used. In addition to its usefulness to treat and prevent influenza in the community, evidence is also emerging supporting the activity of this agent against the H5N1 avian influenza virus. Ongoing studies are further exploring the effectiveness of oseltamivir and other NIs in the management of influenza pandemics.

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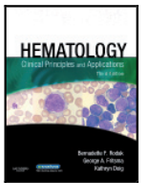

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This comprehensive text examines normal hematopoiesis through diseases of erythroid, myeloid, lymphoid and megakaryocytic origins. Hemostasis and coagulation theory, testing, and instrumentation are also thoroughly discussed. Beautiful full-color illustrations throughout the text enhance comprehension and allow students to realistically visualize hematology concepts.

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