ZANAMIVIR

Introduction

Zanamivir (trade name in Australia "**Relenza"**) is an **inhalational** antiviral **neuraminidase inhibitor** drug used for the treatment and prevention of **influenza.**

Influenza viral replication is confined to the **superficial epithelium** of **the respiratory tract**.

The activity of **zanamivir** is extracellular; it inhibits the release of infective influenza virions from the epithelial cells of the respiratory tract, thereby reducing the propagation of both influenza A and B viruses.

The efficacy of zanamivir following inhalation to the respiratory tract has been confirmed in clinical studies.

As zanamivir is **inhaled**, its use is precluded by people unable to effectively use inhalers (and so will require treatment with **orally** administered **oseltamivir**).

Zanamivir has some *theoretical* advantage over oseltamivir in pregnant women as there is little systemic absorption of the drug. [2] There is however more *clinical experience* with the use of oseltamivir in pregnancy. [4]

As zanamivir is not significantly systemically absorbed, oral oseltamivir may be a better option in patients who are significantly systemically unwell e.g. hypotensive, although **IV** therapy with zanamivir (or peramivir) may be the best option in very unwell patients.

Solution for injection or nebulisation is not marketed in Australia but may be available through the Special Access Scheme

Indications include:

- The treatment of influenza A, within 48 hours of the onset of illness
- The treatment of influenza B, within 48 hours of the onset of illness
- Prophylaxis of influenza A and B

In patients with severe illness / immunocompromise however treatment may be given after 48 hours (e.g. up to 4 days).

The neuraminidase inhibitors can:

- Reduce the duration of symptoms
- Reduce the severity and complications
- Reduce infectivity of infected patients.
- Help prevent infection in uninfected subjects.

The earlier treatment starts, the shorter and less severe the illness.

In young individuals without risk factors, such as pregnancy, immunocompromise, or significant comorbidities the one to two days of symptomatic relief zanamivir gives is probably not worth the cost of the evolution of viral resistance. Zanamivir is therefore probably best reserved for those with significant risk factors and/ or who are significantly unwell.

Oseltamivir is an orally active alternative within the neuraminidase inhibitor group

History

Zanamivir was developed in 1989 by Australian scientists **Peter Colman** and **Joseph Varghese** at the Australian CSIRO, in collaboration with the Victorian College of Pharmacy, and Monash University.

Zanamivir was the first of the neuraminidase inhibitors, and the first effective antiviral agent for the treatment of influenza.

Oseltamivir was developed a few months after zanamivir, by Gilead Sciences, an American biopharmaceutical company.

Both zanamivir and oseltamivir were approved for the treatment of influenza A and B in the US and Europe in 1999.

Chemistry

It was known as early as 1974 that 2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid (DANA), a sialic acid analogue, was an inhibitor of neuraminidase

Zanamivir is 4-Guanidino (GU) - DANA, an analogue of the DANA molecule.

Classification

Anti-Influenza virus agents include:

1. Neuraminidase inhibitors:
    - Oseltamivir (oral)

- **Zanamivir (inhaled or IV)**
- Peramivir (IV)

2. Endonuclease inhibitors

- Baloxavir (oral)

Preparations

Zanamivir as:

"Diskhaler" inhalation device:

- 5 mg/dose (= 5 mg per disk), (20 doses)

  This is in the form of powder for inhalation

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Mechanism of Action

Zanamivir is a selective **neuraminidase inhibitor**

Neuraminidase enzymes are glycoproteins found on the virion surface.

Viral neuraminidase is essential for the release of recently formed virus particles from infected cells and the further spread of infectious virus in the body.

Neuraminidase inhibitors inhibit the viral surface enzyme neuraminidase, preventing the **release of new virus** from infected cells.

Pharmacodynamics

The neuraminidase inhibitors can:

- Reduce the duration of symptoms
- Reduce the severity and complications
- Reduce infectivity of infected patients.
- Help prevent infection in uninfected subjects.

Treatment is generally thought to be of greatest benefit if commenced early (ideally within 48 hours of symptom onset), and if targeted to people at highest risk of complications.

The earlier treatment starts, the shorter and less severe the illness.

Note that, as for all antivirals, the prevalence of viral resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.

Resistance to zanamivir is rare; while it develops much more easily to oseltamivir and has been associated with treatment failure. [6]

Resistant strains may spread to contacts. As susceptibility to anti-virals rapidly changes, it is important to be aware of the circulating influenza virus strains and their resistance patterns.

Pharmacokinetics

Absorption:

- Zanamivir is administered by inhalation. An IV preparation is also available.

  After oral inhalation, zanamivir is widely deposited in the respiratory tract mucosa, thus delivering the drug to the site of the influenza infection.

- Despite a relatively large proportion of the inhaled dose being swallowed, the absolute oral bioavailability of swallowed zanamivir is low (about 2%) and so the swallowed drug does not result in any significant systemic exposure.

Distribution

- Protein binding (of systemically absorbed zanamivir is low at < 10%
- Zanamivir is thought likely to be able to cross the human placenta.
- Zanamivir is thought likely to be excreted into human breast milk.

Metabolism and excretion:

- Zanamivir does not undergo metabolism. It is excreted as unchanged drug.
- The delayed serum half-life following oral inhalation (range 2.5 - 5.1 hours) reflects slow systemic absorption by this route.
- Half-life is around 2.5 - 5.0 hours.

Indications

These include:

1. The treatment of influenza A, within 48 hours of the onset of illness

2. The treatment of influenza B, within 48 hours of the onset of illness

3. Where **severe** illness is already present, or the patient has significant immunocompromise treatment should be offered **regardless of the patient's risk group or duration of symptoms**. [1]

   High risk groups include:

   - Pregnant women
   - The morbidly obese
   - Those with underlying chronic diseases (especially asthma and respiratory diseases, but also chronic cardiac, renal, metabolic and neurological disorders)
   - The immunosuppressed
   - Homeless people
   - Indigenous Australians
   - The elderly (more than 65 years and nursing home patients) and the very young (less than 5 years).

4. Prophylaxis of influenza A and B

   - These drugs may be used as prophylaxis in institutions (eg hospitals or aged care facilities) or in the community during outbreaks of novel strains of influenza. [1]
   - It should be noted that **vaccination** is the preferred option for preventing influenza.

Contra-indications/precautions

These include:

1. Airways disease, if severe:

   - e.g. asthma bronchospasm or worsening respiratory function may occur.

2. Zanamivir inhalation powder must not be made into an extemporaneous solution for administration by nebulisation or mechanical ventilation.

3. Zanamivir should not be prescribed to patients incapable of using the inhaler device adequately.

Pregnancy

Zanamivir is classified as a category B1 drug with respect to pregnancy, (as is oseltamivir).

Class B1 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

From the limited information available, maternal use of zanamivir has not been associated with an increased risk of congenital malformations or adverse pregnancy outcomes.

Zanamivir is considered safe to use during pregnancy.

Zanamivir has some *theoretical* advantage over oseltamivir in pregnant women as there is little systemic absorption of the drug. [2] There is however more *clinical experience* with the use of oseltamivir in pregnancy. [4]

Breast feeding

Published reports describing the use of zanamivir during breastfeeding have not been located.

Zanamivir is poorly absorbed when taken orally, and infants exposed to zanamivir via breast milk are unlikely to experience adverse effects.

Therefore, zanamivir is considered safe to use during breastfeeding.

Adverse Effects

The main potential problem appears to be bronchospasm.

There have been some reports of patients being treated for influenza who have experienced bronchospasm and/or decline in respiratory function after the use of zanamivir.

The decline in respiratory function is considered to be possibly related to zanamivir although the causal relationship is difficult to assess as influenza infection can be associated with increased airways hyper-responsiveness, and in some patients concurrent medical conditions were present.

Patients should have a fast acting bronchodilator available.

Patients scheduled to take inhaled bronchodilators at the same time as zanamivir should be advised to use their bronchodilators before taking inhaled zanamivir

Note that there is a warning in the product information regarding an association between zanamivir and neuropsychiatric symptoms; however, at present, evidence suggests that these rare events are more likely to be due to **influenza** rather than zanamivir. [2]

Dosing

Prevention of influenza:

Begin treatment within 36 hours of exposure (close contact with an infected person).

Adult, child 5 years and over,:

- Dry Powder Inhaler (DPI) 2 inhalations (i.e 10 mg) once daily for 10 days.
- This may be extended up to 28 days if necessary.

Treatment of influenza:

Start treatment as early as possible after symptoms occur, but not > 48 hours after onset of initial symptoms of infection.

In severe illness, however, **later treatment**, e.g. within 4 days of onset, is of some benefit.

- Adult, child 5 years and over, DPI 2 inhalations (10 mg) twice daily for 5 days.

Appendix 1

Device for dry powder inhalation of zanamivir.

References

1. eTG - July 2017

2. Zanamivir in Australian Medicines Handbook Website Accessed, October 2017.

3. Zanamivir in MIMs Website, 1 November 2013.

4. Zanamivir in RWH Pregnancy & Breastfeeding Guidelines; 17 January 2017.

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