Antiviral management of Influenza A (H1N1) in critical care

Meera Thacker
Rob Shulman
Mike Kidd
Mark Borthwick
## Contents

**REFERENCES** ............................................................................................................................................................... 20  
**RIBAVIRIN TREATMENT** .......................................................................................................................................... 17  
**ZANAMIVIR (RELENZA®) TREATMENT** ................................................................................................................ 9  
**OSELTAMIVIR (TAMIFLU®) TREATMENT** ................................................................................................................ 4  

**INTRODUCTION** ............................................................................................................................................................... 3  

**OSELTAMIVIR (TAMIFLU®) TREATMENT** ................................................................................................................ 4  

**B** BACKGROUND ............................................................................................................................................................... 4  
**C** CLINICAL EVIDENCE...................................................................................................................................................... 4  

*Case Reports in Haemofiltration Patients:* ...................................................................................................................... 4  

*Combination with probenecid:* .......................................................................................................................................... 5  
**A** ADMINISTRATION AND DOSING SCHEDULE ............................................................................................................ 5  
**C** CLINICAL PHARMACOKINETICS ..................................................................................................................................... 6  
**R** RENAL IMPAIRMENT .................................................................................................................................................... 6  
**H** HEPATIC IMPAIRMENT ................................................................................................................................................ 7  
**S** SIDE EFFECTS ................................................................................................................................................................ 7  
**D** DRUG INTERACTIONS .................................................................................................................................................... 8  
**M** MONITORING TREATMENT EFFICACY............................................................................................................................... 8  
**D** DRUG RESISTANCE ........................................................................................................................................................ 8  
**S** SUMMARY ..................................................................................................................................................................... 8  

**ZANAMIVIR (RELENZA®) TREATMENT** ................................................................................................................ 9  

**B** BACKGROUND ............................................................................................................................................................... 9  
**C** CLINICAL EVIDENCE...................................................................................................................................................... 9  
**P** PLACE IN THERAPY ........................................................................................................................................................ 10  
**A** ADMINISTRATION AND DOSING SCHEDULE ............................................................................................................ 10  
**C** CLINICAL PHARMACOKINETICS ..................................................................................................................................... 11  
**R** RENAL AND HEPATIC IMPAIRMENT ............................................................................................................................... 11  
**S** SIDE EFFECTS ................................................................................................................................................................ 12  
**P** PRECAUTIONS .............................................................................................................................................................. 12  
**D** DRUG INTERACTIONS .................................................................................................................................................... 12  
**D** DRUG RESISTANCE ........................................................................................................................................................ 13  
**M** MONITORING TREATMENT EFFICACY............................................................................................................................... 13  
**S** SUMMARY ..................................................................................................................................................................... 13  

**PERAMIVIR TREATMENT** .............................................................................................................................................. 14  

**B** BACKGROUND ............................................................................................................................................................... 14  
**C** CLINICAL EVIDENCE...................................................................................................................................................... 14  
**P** PLACE IN THERAPY ........................................................................................................................................................ 14  
**A** ADMINISTRATION AND DOSING SCHEDULE ............................................................................................................ 14  
**C** CLINICAL PHARMACOKINETICS ..................................................................................................................................... 15  
**R** RENAL AND LIVER IMPAIRMENT ............................................................................................................................... 15  
**S** SIDE EFFECTS ................................................................................................................................................................ 16  
**D** DRUG INTERACTIONS .................................................................................................................................................... 16  
**D** DRUG RESISTANCE ........................................................................................................................................................ 16  
**S** SUMMARY ..................................................................................................................................................................... 16  

**RIBAVIRIN TREATMENT** ............................................................................................................................................... 17  

**B** BACKGROUND ............................................................................................................................................................... 17  
**C** CLINICAL EVIDENCE...................................................................................................................................................... 17  
**P** PLACE IN THERAPY ........................................................................................................................................................ 18  
**A** ADMINISTRATION AND DOSING SCHEDULE ............................................................................................................ 18  
**C** CLINICAL PHARMACOKINETICS ..................................................................................................................................... 18  
**R** RENAL AND LIVER IMPAIRMENT ............................................................................................................................... 18  
**S** SIDE EFFECTS ................................................................................................................................................................ 19  
**P** PRECAUTIONS .............................................................................................................................................................. 19  
**D** DRUG INTERACTIONS .................................................................................................................................................... 19  
**D** DRUG RESISTANCE ........................................................................................................................................................ 19  
**S** SUMMARY ..................................................................................................................................................................... 19  

**REFERENCES** ...................................................................................................................................................................... 20
Summary

Oseltamivir Summary

- Oseltamivir is currently first line therapy for treating influenza in critically ill patients.
- Reports of the use of high dose prescribing for a longer duration (150mg twice daily up to 10 days) in the critically ill population on intensive care units is being considered globally.
- There is limited evidence on appropriate dosing in patients on haemofiltration.
- There is little potential benefit of probenecid + oseltamivir in critically ill patients, whilst oseltamivir supplies are plentiful.
- The main adverse effects that need to be monitored are severe headaches and persistent vomiting.
- In the clinical setting, oseltamivir resistant viruses are associated with the use of the drug as prophylaxis in patients, even if full treatment doses are subsequently used
- In pregnancy, oseltamivir 75mg twice daily may be used where inhaled zanamivir is unsuitable or contraindicated.

Zanamivir Summary

- Zanamivir should be considered the treatment of choice in critically ill patients who:
  - are not absorbing from the gastrointestinal tract
  - fail to clear oseltamivir-sensitive virus despite treatment
  - have oseltamivir-resistant virus
  - are pregnant (inhaled only). If mechanically ventilated and pregnant, use oseltamivir. If also not absorbing then consider intravenous (unlicensed) zanamivir, if benefit outweighs the risk.
- Inhaled zanamivir is suitable for non mechanically ventilated patients. However in mechanically ventilated patients, intravenous zanamivir is indicated.

Peramivir Summary

Peramivir is currently unavailable in the UK. But should this change, it potentially could have a role as an unlicensed alternative to IV zanamivir in those who:
- are not absorbing from the gastrointestinal tract
- fail to clear oseltamivir-sensitive virus despite treatment
- have oseltamivir-resistant virus

Ribavirin Summary

The use of ribavirin is controversial because of the lack of a robust evidence base and safety concerns regarding the potential to cause haemolytic anaemia in patients and reproductive risks to both patient and health care workers. Ribavirin may be considered in critically ill patients who:
- fail to clear zanamivir-sensitive virus despite zanamivir treatment
- have oseltamivir and zanamivir resistant virus
Introduction

Thacker M*, Shulman R**, Kidd IM***, Borthwick M****

*Lead Pharmacist – Critical Care, Royal Free Hospital, **Lead Pharmacist – Critical Care, University College Hospital, ***Consultant Virologist, University College Hospital, ****Consultant Pharmacist – Critical Care, John Radcliffe Hospital

The current treatment options in the UK for new pandemic influenza A (H1N1) are oseltamivir (Tamiflu®) and zanamivir (Relenza®). Both drugs are selective inhibitors of neuraminidase (NA), a major influenza virus surface enzyme which is critical for release of newly-replicated influenza virus from the cell. The influenza virus envelope exhibits another important antigenic protein, the haemagglutinin (HA) which is responsible for the initial attachment of the virus to a cell at the start of the infection cycle. Currently, there are 16 known HA subtypes (H1 –H16) and 9 different NA subtypes (N1-N9).

The information below is intended to support prescribing and decision making for antiviral neuraminidase inhibitors in critically ill patients on the Intensive Care Unit (ICU) and may change as more clinical experience and published data become available.

Note that both drugs are also effective against infection with influenza B; a related influenza virus which also causes outbreaks during the winter months.
Oseltamivir (Tamiflu®) Treatment

Background

Oseltamivir is a neuraminidase (NA) inhibitor which is licensed for the prophylaxis and treatment of influenza. It is a potent and selective inhibitor of influenza A NA subtypes. The licensed dose for adults, adolescents and children (>40kg) is 75mg twice a day. In response to the current H1N1v 2009 pandemic, the Health Protection Agency (HPA) have issued a clinical practice note on managing adult critically ill cases and recently in August 2009, the World Health Organisation (WHO) has also issued guidelines on the pharmacological management of pandemic H1N1v 2009. Both report that clinicians have doubled the licensed dose of oseltamivir to treat critically ill patients on the intensive care unit, and have used a longer duration of treatment depending on clinical response. This approach to treatment appears to have been made on the basis that critically ill patients have (i) higher viral loads, (ii) reduced drug concentration in damaged tissue, (iii) reduced absorption of the drug and (iv) greater volumes of distribution.

Clinical Evidence

Below is a summary of the published literature on the use of higher doses in healthy adults.

A randomized controlled trial was performed in 726 previously healthy adults presenting with febrile influenza-like illness. The patients were divided into three treatment arms and randomised to receive either oseltamivir 75mg twice daily, 150mg twice daily or placebo twice daily for 5 days. Of the 726 patients randomised, 475 had confirmed influenza infection. The median duration of illness was significantly shorter in the treatment groups (75mg (median duration of 29h), 150mg (median duration of 35h)) compared to placebo (median duration of 116.5h). The main adverse effects reported in the trial were nausea and vomiting. These effects were more frequent in the oseltamivir groups than placebo and generally occurred at the start of treatment, resolving within 1-2 days.

A similar trial was performed in 629 adults with febrile respiratory illness. This was a double-blind placebo-controlled study where patients were randomised to receive either oseltamivir 75mg twice daily (n=211), 150mg twice daily (n=209) or placebo twice daily (n=209). Of the 629 patients randomised, 374 were infected with influenza. In this group treatment with oseltamivir reduced the duration of illness significantly compared to placebo (75mg (median duration of 71.5hrs), 150mg (median duration of 69.9hrs) placebo (median duration of 103.3hrs). Nausea and vomiting occurred more frequently in the oseltamivir group than placebo and generally occurred at the start of treatment, resolving within 1-2 days.

Case Reports in Haemofiltration Patients:
To date there is very limited information on oseltamivir use in patients on haemofiltration. Below is a summary of 3 case reports to date.

The pharmacokinetic parameters of nasogastrically-administered oseltamivir have also been reported for three patients, presenting with severe H5N1 or H3N2, undergoing haemofiltration. Each patient had been given 150mg twice daily oseltamivir via nasogastric tube within 24 hours of ICU admission. The details for each patient are as follows:

Patient A: Male, 30yr, started oseltamivir 6 days after onset of illness, CVVH ultrafiltration rates 2.75L/h
Patient B: Female, 22 yrs, pregnant, started oseltamivir 7 days after onset of illness; CVVH ultrafiltration rates 2.2L/hr
Patient C: Female 76 yrs, started oseltamivir 8 hrs after onset of illness, CVVH ultrafiltration rates 2L/hr.
Patient A had a severe headache and persistent vomiting when off the ventilator therefore the oseltamivir had to be stopped after 8 days of treatment. Tracheal aspirates went from influenza A positive to negative within 5 days of treatment. The trough concentration of oseltamivir carboxylate (OC), the active metabolite, was 376 ng/ml.

Patient B had tracheal aspirates, pleural fluid, stool and plasma which were influenza A H5N1 positive 1 day after starting treatment. The trough concentration of OC was 575 ng/ml.

Patient C: Nasal swabs went from influenza A H3N2 positive to negative after 5 days of treatment. The trough concentration of OC was 2730 ng/ml.

For all three patients the dose of 150mg twice daily was found to produce trough concentrations ranging between 376 – 2730 ng/ml. These exceeded the H5N1 IC$_{50}$ MIC (0.69ng/ml). This does show that high trough levels of OC are achieved after 150mg twice daily doses. Dosing decisions have been very difficult in this group of patients and ideally one would recommend drug level monitoring in these patients to minimise toxicity and resistance developing. Refer to the renal impairment section further in the document for dosing guide in this patient group.

Combination with probenecid:

There have been some discussions on the use of oseltamivir used in combination with probenecid. Unless oseltamivir supplies become limited, there is no real benefit of using probenecid in critically ill patients. Probenecid is known to inhibit renal tubular urate resorption and to decrease the excretion of several medications including oseltamivir. The co-administration of a single 150 mg dose of oseltamivir and probenecid (500 mg orally four times a day for 4 days) resulted in steady-state oseltamivir carboxylate concentrations that were 2.5-fold higher than those achieved with oseltamivir administration alone. This combination has not been extensively studied, only in healthy volunteers so at present it would not be considered for mainstream use. However it may be an option if supplies of oseltamivir are limited. It should be noted that probenecid interacts with several drugs used in critical care and it may increase concentrations of meropenem, rifampicin, aciclovir, some quinolones, lorazepam and paracetamol. Lower doses of thiopentone may be required and it may increase the speed of induction with midazolam.

---

**Administration and dosing schedule**

**Presentation:** Oseltamivir (as phosphate) 30mg, 45mg, 75mg capsules

**Treatment doses in adults:** 150mg twice a day for up to 10 days have been advocated. In pregnancy the WHO state that there is insufficient safety data for doses higher than 75 mg twice daily.

**Administration via nasogastric tube:**
- Stop enteral feed.
- Flush enteral feeding tube with the recommended volume of water.
- Empty the contents of the capsule into a medicine pot.
- Add 5mL of water and stir to mix thoroughly.
- Draw the dispersion into an appropriate enteral syringe taking care to draw up all particles.
- Flush this via the feeding tube.
- Add another 5mL of water to the medicine pot, stir and draw into the syringe. This will ensure no residual dose remains in the pot.
- Flush this via the feeding tube.
- Finally, flush with the recommended volume of water.
- Re-start the feed, unless a prolonged break is required.
Clinical Pharmacokinetics

Oseltamivir is readily absorbed from the gastrointestinal tract and is converted by hepatic esterases to the active metabolite oseltamivir carboxylate (OC). The bioavailability of the OC from orally administered oseltamivir phosphate is 80%. OC is detectable in plasma within 30 minutes and reaches maximal concentrations after 3 to 4 hours. After peak plasma concentrations are reached, the half life of OC declines within 6 to 10 hours. OC is largely renally cleared by glomerular filtration and renal tubular excretion. The half life extends to 36 hours in patients with end stage renal failure. Oseltamivir phosphate is 42% bound to plasma proteins; OC is 3% bound to plasma proteins. The mean volume of distribution of OC is approximately 23 litres and it has a sieving coefficient of 1.11

Renal Impairment

There is very limited data on the use of oseltamivir in critically ill patients. Below is a guide to assist dosing for treatment and prophylaxis of oseltamivir for H1N1 for critically ill adults with renal impairment.12

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Recommended treatment dose (usually for 5 days but prolonged courses needs to be discussed with Virology).</th>
<th>Recommended prophylaxis dose (usually for 10 days but prolonged courses needs to be discussed with Virology).</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30ml/min</td>
<td>75mg -150mg BD*</td>
<td>75mg OD</td>
</tr>
<tr>
<td>&gt;10 to 30ml/min</td>
<td>75mg OD to BD *</td>
<td>75mg every second day</td>
</tr>
<tr>
<td>&lt;10ml/min</td>
<td>75mg STAT * repeated every 5 days if required</td>
<td>75mg STAT every 7 days (usually 2 doses)</td>
</tr>
<tr>
<td>Continuous Veno-Venous Haemofiltration (CVVH)</td>
<td>75mg BD</td>
<td>75mg OD</td>
</tr>
</tbody>
</table>

* This has been amended from the usual renal impairment doses that is recommended in the literature, and has been extrapolated from the double doses (150mg BD) that are used in the critically ill population. There are no clinical trials at the time of this document using these doses.

** Prophylaxis may be considered for a patient, when a staff member/relative who is infectious following H1N1 exposure, was found to be in close contact with a critically ill patient.
**Hepatic Impairment**

No dose adjustment necessary, even in moderate hepatic impairment. To date there is no information in acute liver failure and severe hepatic impairment.

**Side Effects**

In adults, the most commonly reported adverse drug reactions (ADRs) were vomiting and nausea in the treatment studies, and nausea and headache in the prevention studies. The majority of these ADRs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. In children, the most commonly reported adverse drug reaction was vomiting.2

**Further post marketing surveillance data on selected serious adverse drug reactions**

(This is information from the medicines compendium and has been included in this information pack to ensure the awareness of adverse effects that have been reported)2

- **Immune system disorders**: Frequency not known: hypersensitivity reactions, including anaphylactic/anaphylactoid reactions.

- **Psychiatric disorders and nervous system disorders**: Frequency not known: In patients with influenza who were receiving oseltamivir, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares). These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. The contribution of oseltamivir to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir.

- **Eye disorders**: Frequency not known: visual disturbance.

- **Cardiac disorders**: Frequency not known: cardiac arrhythmia.

- **Gastrointestinal disorders**: Frequency not known: gastrointestinal bleeding and hemorrhagic colitis.

- **Hepato-biliary disorders**: Frequency not known: hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.

- **Skin and subcutaneous tissue**: Frequency not known: severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and angioneurotic oedema.
Drug Interactions

Oseltamivir phosphate and its active metabolite, OC, are not metabolised by and do not inhibit cytochrome P-450 isoenzymes; interactions with drugs that are substrates for or inhibitors of these enzymes are unlikely.\(^2\)

Monitoring treatment efficacy

There are no formal recommendations for how to assess whether oseltamivir is working, and at the time of writing there are no routinely-available therapeutic drug monitoring services for determining drug levels. However a general approach based on monitoring influenza virus load by reverse-transcriptase polymerase chain reaction (RT-PCR) of respiratory tract samples can be suggested. Firstly, bronchial lavage samples (either non-directed or broncho-alveolar) should be taken at least 5-day intervals, whenever a new 5-day course of drug is commenced, or whenever a drug change is instigated. A fall in relative viral load of approximately 100-fold between two such samples – tested in the same assay run – would likely indicate an antiviral effect and be expected to accompany a clinical improvement in the patient’s condition. Where a fall in relative viral load is not evident, and a patient is not suspected to have gastric problems which might limit absorption, then virology laboratory investigations should be conducted to rule out development of antiviral resistance.

As a general infection control rule, critically-ill patients should have two consecutive negative RT-PCR results before being brought out of respiratory isolation.

Drug Resistance

Influenza A can become resistant to oseltamivir due to naturally-occurring point mutations in the neuraminidase gene. A cytosine -> thymidine change results in the substitution of tyrosine (encoded by T-A-C) for histidine (encoded by C-A-C) at amino acid position 274, which confers high-level resistance to oseltamivir in N1-subtype influenza viruses. Such resistant viruses remain fully sensitive to zanamivir. In the clinical setting, oseltamivir resistant viruses are associated with the use of the drug as prophylaxis in patients, even if full treatment doses are subsequently used.

Summary

- Oseltamivir is currently first line therapy for treating influenza in critically ill patients.
- Reports of the use of high dose prescribing for a longer duration (150mg twice daily up to 10 days) in the critically ill population on ICU is being considered across the globe.\(^1^4\)
- There is limited evidence on appropriate dosing patients on haemofiltration.
- There is little potential benefit of probenecid and oseltamivir in critically ill patients, whilst oseltamivir supplies are plentiful.
- The main adverse effects that need to be monitored are severe headaches and persistent vomiting.
- In the clinical setting, oseltamivir resistant viruses are associated with the use of the drug as prophylaxis in patients, even if full treatment doses are subsequently used
- In pregnancy, oseltamivir 75mg twice daily may be used where inhaled zanamivir is unsuitable or contraindicated.
Zanamivir (Relenza®) Treatment

Background

Zanamivir is also a neuraminidase (NA) inhibitor which is licensed for the prophylaxis and treatment of influenza in adults and children (>5 years). The licensed method of administration for zanamivir for treatment of H1N1 is via dry powder inhalation using a diskhaler device and it is given at a dose of 10mg BD, which actually delivers 8mg. It has very poor oral bioavailability when administered via the gastrointestinal tract (GIT) and so can not be given by this route. The diskhaler may only be used in patients who are self ventilating. In mechanically ventilated patients where it is not possible to administer the drug via diskhaler; although there was initial interest in nebulised zanamivir for use in those unable to absorb oseltamivir. However, the FDA has recently released a warning notice and this has stated that zanamivir powder should not be used via the nebulised route and the Department of Health have reinforced this advice. This emerged following an incident where nebulised zanamivir prepared from the licensed product caused a mechanical ventilator to block, which in turn lead to the death of a patient. The zanamivir powder is formulated in lactose which was implicated as the causative factor in this event. This document describes how zanamivir may be administered intravenously or inhaled via the diskhaler. It also summarises the data available with nebulised zanamivir; notwithstanding the recent recommendations against its use. Zanamivir has a role in H1N1 patients who are unable to absorb oseltamivir from the GIT or have failed to clear the virus (as evidenced by PCR analysis) despite treatment with oseltamivir. Genotypic resistance to oseltamivir is of course one potential cause of oseltamivir treatment failure, and should be investigated as a possibility.

Clinical Evidence

Studies of the unlicensed IV zanamivir preparation 600mg at a dose of 12-hourly have been sparse but high drug penetration has been demonstrated in the respiratory mucosa of human volunteers, following experimental human influenza A virus inoculation. This product and dose were used successfully in a case of H1N1 that was refractory to a course of nebulised zanamivir. Zanamivir aqueous solution which can be administered via inhaled nebulized and intravenous routes are available on a compassionate use basis, but supplies of this are very limited. The IV product should be avoided in pregnancy, unless the expected benefit to the patient is thought to outweigh any possible risk to the fetus. The safety of zanamivir when used during pregnancy has not been established. Reproductive studies performed in rats and rabbits indicated that placental transfer of zanamivir occurs. Studies in rats did not show any evidence of teratogenicity, impairment of fertility or clinically significant impairment of peri or post-natal development of offspring following administration of zanamivir. However, there is no information on placental transfer in humans.

A double-blinded, randomized, placebo controlled trial was conducted in 41 patients to assess the tolerability and efficacy of nebulised zanamivir (16mg four times a day) in combination with rimantadine. The length of treatment for both treatment and placebo arms was 5 days. The median time to viral shedding was 4 days in the rimantadine/placebo arm and 2 days in rimantadine/zanamivir arm. Only one of the patients had an adverse drug event (retrosternal burning with dyspnoea) thought to be attributable to the study medication. Note that whilst the majority of the viruses in the study were sensitive to rimantadine, the current H1N1 influenza is rimantadine-resistant. This trial did show, however, that higher nebulised of doses of zanamivir were well tolerated.

A placebo controlled pilot treatment study of adults (unpublished) was conducted to evaluate the safety and efficacy of zanamivir administered via nebuliser (16mg dose) and intranasally (6.4mg dose) twice daily for 7 days. Patients were divided into three groups: Group 1 received zanamivir (16mg) via nebuliser plus zanamivir (6.4mg) via nebuliser.
(6.4mg) intranasally, Group 2 received zanamivir (16mg) via nebuliser plus placebo intranasally and Group 3 received both placebos via nebuliser and intranasally. Due to a low incidence of influenza, the targeted recruitment was not achieved. The study, therefore, did not have sufficient power to detect a specific treatment difference. Although the study lacked sufficient power, some useful data on safety and tolerability did emerge. The most frequently reported drug adverse events in the inhaled zanamivir (group 2) were dizziness (5%), nausea and vomiting (11%). Only one serious event (severe frontal headache and dizziness) was reported and deemed possibly related zanamivir. In summary, higher dose of nebulised zanamivir were well tolerated. 22

**Place in therapy**

Zanamivir should be considered the treatment of choice in critically ill patients who

- are not absorbing from the GIT
- fail to clear oseltamivir-sensitive virus despite treatment
- have oseltamivir-resistant virus
- are pregnant (inhaled only), if oseltamivir is contra-indicated, and the benefit outweighs the risk

**Administration and dosing schedule**

**Presentation** 5mg/dose, inhalation powder, Vials (unlicensed 200mg/20ml) no refrigeration required.

**Adults**

**Treatment dose**

For non-mechanically ventilated patients, inhale via the diskhaler 10mg twice daily

**Prophylaxis dose**

For non-mechanically ventilated patients, inhale via the diskhaler 10mg once daily

**Nebulised** This route would not appear to offer any advantages to the IV route. The diskhaler product should not be used for nebulisation.17 There is unlicensed aqueous solution of the drug that does not contain lactose available from GlaxoSmithKline for compassionate use in severe influenza illness. This can be used either for nebulisation at a dose of 25mg 6-hourly or intravenously at 600mg 12-hourly. If this formulation is used for nebulisation, each vial can be multi-used for up to 24 hours (i.e.4 doses), if refrigerated.20

**Intravenous** The unlicensed IV product can be obtained on a compassionate patient-specific basis from GlaxoSmithKline (0800 221 441). To prepare, withdraw the required zanamivir dose into a syringe. Remove the same volume from an infusion bag of sodium chloride 0.9%. Add the zanamivir to the infusion bag and mix gently by hand and administer over 30 minutes. In cases of volume overload or paediatrics, the final concentration of zanamivir administered should NOT be lower than 0.2mg/mL. For patients on intermittent hemodialysis, the dose of zanamivir is administered after completion of haemodialysis.20
Clinical Pharmacokinetics

Zanamivir is not protein bound and not hepatically metabolised or modified. It is excreted unchanged in the urine.\textsuperscript{15}

Renal and Hepatic impairment

No dose is adjustment necessary, except for the IV regimen. Please read the dosing instructions below very carefully.

The table below shows the twice daily maintenance dose regimens of IV Zanamivir for adults and adolescents, which is administered following an initial dose of 600 mg.\textsuperscript{20}

<table>
<thead>
<tr>
<th>ClCr (mL/min)</th>
<th>Adults and Adolescents</th>
<th>≥ 80</th>
<th>50 to &lt;80</th>
<th>30 to &lt;50</th>
<th>15 to &lt;30 &amp; CVVF</th>
<th>&lt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 mg</td>
<td>400 mg</td>
<td>250 mg</td>
<td>150 mg</td>
<td>60 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time interval between initial dose and maintenance dose

- The twice daily maintenance dose regimen should begin 12 hours after starting the initial dose infusion, except for patients in the renal failure categories below:
- For patients with ClCr of 15 to <30 mL/min or haemofiltration (CVVF), the twice daily dose regimen should begin at 24 hours after the start of the initial dose.
- For patients with ClCr of <15 mL/min, the twice daily dose regimen should begin at 48 hours after start of the initial dose.

For pregnant women, pre-pregnancy body weight should be used in the calculation of ClCr.

IV Zanamivir Dosage Determination for Children (≥ 6 months of age):

- Assess renal function by determination of creatinine clearance (ClCr, in mL/min/1.73 m\(^2\)), which may be calculated from height and serum creatinine, as follows:

  For serum creatinine in units of mg/dL:

  \[
  CLCr(\text{mL} / \text{min}/1.73m^2) = \frac{0.55 \cdot HT}{Scr}
  \]

  where HT = height in cm and Scr = serum creatinine in mg/dL.

  For serum creatinine in units of micromoles/liter:

  \[
  CLCr(\text{mL} / \text{min}/1.73m^2) = \frac{48.6 \cdot HT}{Scr}
  \]

  where HT = height in cm and Scr = serum creatinine in \(\mu\text{M}\).
Based on the CLcr determination and body weight, children should receive IV zanamivir doses (mg/kg) ranging from 1.5 to 24 mg/kg twice daily, as shown:

<table>
<thead>
<tr>
<th>Paediatrics (≥6 months)</th>
<th>CLcr (mL/min/1.73m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Range</td>
<td>≥ 80</td>
</tr>
<tr>
<td>19 to 37 kg ^1</td>
<td>16 mg/kg</td>
</tr>
<tr>
<td>11 to &lt;19 kg</td>
<td>20 mg/kg</td>
</tr>
<tr>
<td>&lt;11 kg</td>
<td>24 mg/kg</td>
</tr>
</tbody>
</table>

^1 Children who are less than 13 years of age but who weigh >37kg should receive the recommended dose for adults and adolescents.

**Side Effects**

There have been rare reports of patients with previous history of respiratory disease (asthma, COPD) and very rare reports of patients without previous history of respiratory disease, who have experienced acute bronchospasm and/or serious decline in respiratory function after use of zanamivir.\(^{15}\)

The adverse events considered at least possibly related to the treatment are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000).

**Immune system disorders:** Very rare: allergic-type reaction including facial and oropharyngeal oedema

**Respiratory, thoracic and mediastinal disorders:** Very rare: bronchospasm, dyspnea, throat tightness or constriction

**Skin and subcutaneous tissue disorders:** Very rare: rash, urticaria

**Psychiatric and nervous system disorders:** Convulsions and psychiatric events such as depressed level of consciousness, abnormal behaviour, hallucinations and delirium have been reported during zanamivir administration in patients with influenza. The symptoms were mainly reported in children and adolescents. Convulsions and psychiatric symptoms have also been reported in patients with influenza not taking zanamivir.\(^{18}\)

**Precautions**

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. This does not apply to the lactose free formulations available on a compassionate use basis.

Neuropsychiatric events have been reported during administration of zanamivir in patients with influenza, especially in children and adolescents. Therefore, patients should be closely monitored for behavioural changes and the benefits and risks of continuing treatment should be carefully evaluated for each patient.\(^{15}\)

**Drug Interactions**

Zanamivir is not protein bound and not hepatically metabolised or modified. Clinically significant drug interactions are unlikely.\(^{15}\)
Drug Resistance

Surveillance of seasonal influenza in Australia and south-east Asia during 2006-8 detected a small number of influenza A H1N1 strains which had a significantly reduced susceptibility to zanamivir and determined by an amino acid substitution Q136K. However this arose after passage of the viruses in culture and was not detectable in the original clinical specimens; therefore the true role of this mutation in human infection remains unknown, despite its effect being confirmed by reverse genetics. This mutation does not affect virus susceptibility to oseltamivir.

Monitoring treatment efficacy

This should be done according to the guidance described for oseltamivir (see page 5).

Summary

- Zanamivir should be considered the treatment of choice in critically ill patients who:
  - are not absorbing from the gastrointestinal tract
  - fail to clear oseltamivir-sensitive virus despite treatment
  - have oseltamivir-resistant virus
  - are pregnant (inhaled only). If mechanically ventilated and pregnant, use oseltamivir. If also not absorbing then consider intravenous (unlicensed) zanamivir, if benefit outweighs the risk.
- Inhaled zanamivir is suitable for non mechanical ventilated patients. However in mechanically ventilated patients, intravenous zanamivir is indicated.
Peramivir Treatment

Background

Peramivir is also a neuraminidase inhibitor, and has been made available in the US on an unlicensed basis as an intravenous formulation for emergency use for the treatment of certain hospitalized patients with known or suspected 2009 H1N1 influenza. This drug is still being evaluated in phase 3 clinical trials, though limited phase 2 and 3 safety and efficacy data for peramivir IV are available. At the time of writing, peramivir is not available in the UK but that may change. It is manufactured in the US by BioCryst.

Clinical Evidence

The FDA website states that in common with the other approved neuraminidase inhibitors, the efficacy and safety of IV peramivir has not been established in hospitalized patients with any type of influenza A or B virus including 2009 H1N1 virus. Phase 2 and 3 trials with IV and intramuscular (IM) administration include a statistically significant effect of a single 300 mg IV or 600 mg IV dose of peramivir compared to placebo in adult patients with acute uncomplicated influenza. Additionally, two phase 2 trials and one phase 3 trial, did not show statistically significant treatment differences between peramivir and placebo or oseltamivir. Furthermore in a phase 2 trial of hospitalised adults, IV peramivir 200mg, 400mg or oseltamivir; the results did not show superiority of either peramivir dose over oseltamivir or a dose response for peramivir for the primary endpoint.

To date ~1,891 clinical trials subjects have received peramivir given IV or IM, including 478 who received a single dose of 600 mg IV. Data on multi-dose administration are limited; 33 adult clinical trial subjects have received approximately 600mg (or higher) intravenously once daily for five or more days.

No patients < 18 years have received peramivir in clinical trials. No pharmacokinetic, safety or efficacy data are available in the paediatric population. Despite this, the FDA has permitted a limited use of peramivir IV in children under emergency conditions. Some safety data exists for peramivir IV 600 mg once daily for 5 to 10 days under emergency conditions. No pregnant women have received peramivir to date and no pharmacokinetic, safety or efficacy data are available in pregnancy.

Place in therapy

Peramivir is currently unavailable in the UK. But should this change, it potentially could have a role in those who:

- are not absorbing from the GIT
- fail to clear oseltamivir-sensitive virus despite treatment
- have oseltamivir-resistant virus

Administration and dosing schedule

**Presentation** 200mg/20 ml vials (unlicensed). No refrigeration required.

**Adults**  
**Treatment dose** The standard adult dose of peramivir is 600 mg IV in sodium chloride 0.9% over 30 minutes once a day, for 5 to 10 days. The maximum infusion rate is 40mg/min.

**Paediatric Daily Dosage**

**Recommendations**

14
**Clinical Pharmacokinetics**

The major route of elimination of unchanged peramivir is via the kidney. In normal renal function, the elimination half-life of IV product is 7.7 to 20.8 hour.

**Renal and Liver impairment**

<table>
<thead>
<tr>
<th>Renal Impairment or Hemodialysis Creatinine Clearance</th>
<th>Daily Dose (IV)&lt;sup&gt;24&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Renal Impairment CrCl 50-80 mL/min</td>
<td>600 mg</td>
</tr>
<tr>
<td>Moderate Renal Impairment CrCl 31-49 mL/min</td>
<td>150 mg</td>
</tr>
<tr>
<td>Severe Renal Impairment CrCl 10-30 mL/min</td>
<td>100 mg</td>
</tr>
<tr>
<td>Haemofiltration or CrCl &lt;10 mL/min and not on haemodialysis</td>
<td>100 mg on day 1 followed by 15 mg daily thereafter</td>
</tr>
<tr>
<td>Hemodialysis or CrCl &lt;10 mL/min</td>
<td>100 mg on day 1, then 100 mg given 2 hours after dialysis days only.</td>
</tr>
</tbody>
</table>

For dosing in paediatric renal function consult this FDA site.<sup>24</sup>

As peramivir IV is not significantly metabolized by the liver, no dose adjustment is necessary in impaired hepatic function.<sup>24</sup>
Side Effects

The most commonly reported adverse events in clinical trials of peramivir IV were diarrhoea, nausea, vomiting, and neutropaenia. Although not seen in the trials to date peramivir IV may be associated with rare cases of anaphylaxis and serious skin reactions and a variety of neurological and behavioural symptoms that have been reported with other neuraminidase inhibitors. From the available phase 1, 2 and 3 data the more common adverse events related to administration of peramivir are:

- diarrhoea
- nausea
- vomiting
- neutrophil count decreased

From the available phase 1 and 2 data, other less common adverse events related to administration of peramivir are:

<table>
<thead>
<tr>
<th>Dizziness</th>
<th>Hyperbilirubinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>headache</td>
<td>raised blood pressure</td>
</tr>
<tr>
<td>somnolence</td>
<td>cystitis</td>
</tr>
<tr>
<td>nervousness</td>
<td>ECG abnormalities (prolonged QTc interval observed in one patient in a phase 1 trial)</td>
</tr>
<tr>
<td>insomnia</td>
<td>anorexia</td>
</tr>
<tr>
<td>feeling agitated</td>
<td>proteinuria</td>
</tr>
<tr>
<td>depression</td>
<td>hematuria</td>
</tr>
<tr>
<td>nightmares</td>
<td></td>
</tr>
<tr>
<td>hyperglycemia</td>
<td></td>
</tr>
</tbody>
</table>

Drug Interactions

Limited data exists but peramivir is primarily renally eliminated so coadministration with drugs that reduce renal function or compete for active tubular secretion may increase plasma concentrations of peramivir and/or increase the concentrations of other renally eliminated drugs.

Drug Resistance

No clinical data are available on the development of resistance to peramivir at present.

Summary

If peramivir IV becomes available in the UK, it will represent an alternative to IV zanamivir. It is unclear if either drug offers any advantages over the other.
Ribavirin Treatment

Background

Ribavirin is a guanosine analogue that likely exhibits multiple mechanisms of action, both direct and indirect.\textsuperscript{25} It has a wide spectrum of activity against RNA and DNA viruses, with the oral and nebulised forms being licensed for the treatment of chronic hepatitis C in combination with other agents\textsuperscript{26} and for respiratory syncytial virus (RSV) bronchiolitis in infants and children.\textsuperscript{27} Ribavirin is known to have in vitro activity against influenza viruses and there is increased interest in the compound because of the current pandemic.\textsuperscript{28}

Clinical Evidence

There are numerous small scale studies of ribavirin to treat influenza, mainly via the oral or aerosolised route and these studies have recently been succinctly summarised.\textsuperscript{28} The dose of ribavirin for oral therapy for active infection ranges from 100mg three times daily to a 3.6g loading followed by 1.2g twice daily. Trials utilising these doses have given mixed results. Plasma bilirubin abnormalities were associated with the higher dose regimens (possibly reflecting haemolytic anaemia, a known side effect of the medication).

Several studies of aerosolised ribavirin with an average exposure of 2 to 6 grams over 3 or 4 days resulted in a more rapid reduction in fever and other clinical signs of influenza in the ribavirin groups, although one study found no difference.\textsuperscript{28}

Information on the efficacy of intravenous ribavirin in influenza is even sparser. One study gave a continuous infusion of ribavirin in three patients with either influenza or parainfluenza infections and noted reductions in viral shedding temporally related to the start of the infusion (5mg/kg/hr for 8 hours followed by 1.5mg/kg/hr for 2 to 6 days).\textsuperscript{29} One case series reports on three patients with influenza associated myocarditis who were treated with intravenous ribavirin. Viral shedding was reported to abruptly stop on initiation of ribavirin therapy, however two of the patients died soon after and the third survived for 8 months on an artificial heart.\textsuperscript{30}
**Place in therapy**

Oral and nebulised ribavirin formulations are available in the UK. Intravenous ribavirin formulations are unlicensed. Ribavirin may have a role in those who:
- fail to clear zanamivir-sensitive virus despite zanamivir treatment
- have oseltamivir and zanamivir resistant virus

**Administration and dosing schedule**

**Presentation** Ribavirin 200mg tablets / capsules, 400mg tablets, 40mg/ml oral solution, 6g lyophylisate / 100ml vial for aerosolisation, 1g/10ml ampoules for infusion (unlicensed).

**Treatment dose in adults:**

**Aerosol / Nebulised**

Greatest experience is with the use of a small particle aerosol generator (SPAG) or Aiolos nebuliser. Most studies that examine ribavirin therapy in influenza use this approach and the licensed product for ribavirin aerosol production for treatment of RSV uses the same method to generate 190microg/l air ribavirin concentration.

Dissolve the powder in a minimum of 75ml water for injections in the 100ml vial. The solution should be adequately mixed to ensure complete dissolution. Shake well. When using the SPAG generator, transfer the solution to the clean, sterilised 500ml flask and dilute to a final volume of 300ml with water for injections. When using the Aiolos nebuliser, transfer the solution into an infusion bag and dilute to a final volume of 300ml with water for injections. The final ribavirin concentration should be 20mg/ml.27

Dosing frequencies vary by study. Typically the aerosol was initially delivered for 16 to 18 hours, then for three 4-hour blocks each day for three days. These patients were not receiving mechanical ventilation.31;32

**Intravenous**

There is currently one UK importer of intravenous ribavirin (Virazole) and that is Clinigen UK (01283 494359). The required dose should be diluted in 5% glucose or 0.9% sodium chloride and administered over 30 to 60 minutes. There is no specific direction on the final concentration to use.

A continuous infusion 5mg/kg/hr for 8 hours followed by 1.5mg/kg/hr for 2 to 6 days has been used for influenza infection and generated plasma levels that far exceeded the MIC. This dose is higher than the recognised dose for Haemorrhagic Fever with Renal Syndrome (33mg/kg initial loading dose followed six hours later by 16 mg/kg every 6 hr during 4 days (16 doses), then followed eight hours later by 8 mg/kg every 8 hr for a further 3 days).33

**Clinical Pharmacokinetics**

Clearance of intravenous ribavirin is approx 28% via the renal route with the remainder through metabolism. There is a long terminal half-life due to phosphorylated ribavirin being sequestered intracellularly. Red blood cells do not degrade phosphorylated ribavirin and thus a proportion of the drug may remain in the system until red blood cells are destroyed.34 There is a high volume of distribution.
Renal and Liver impairment

Data on drug clearance in renal or hepatic impairment is sparse. One small study showed a marked reduction in total plasma clearance in patients with renal impairment and a modest reduction in patients with liver impairment. Patients with impaired renal function should be carefully monitored for signs and symptoms of toxicity, such as haemolytic anaemia. No specific dose adjustment recommendations can be made due to the paucity of information. Renal replacement therapies are unlikely to contribute much to drug clearance due to high volumes of distribution.

Side Effects

Pooled safety data described are derived from 5 clinical trials (402 patients) with hemorrhagic fever with renal syndrome or Argentine Hemorrhagic Fever. The doses used were smaller than in case reports for influenza treatment.

Notable differences between the ribavirin and placebo groups respectively were for anaemia (12.1% and 6.1%), hyperbilirubinaemia (6.3% and 1.7%), coma (1.5% and 5.3%), shock (3.6% and 6.1%), renal failure (12.1% and 20.7%) and dialysis (2.5% and 9.9%).

Carcinogenesis and Mutagenesis

In rodent studies there is some evidence that ribavirin can cause mutagenesis. Rodent studies it was concluded that ribavirin was noncarcinogenic.

Reproduction Studies

Ribavirin was found to be teratogenic in several rodent studies although not in baboon studies. It is concluded that ribavirin may cause foetal harm in humans. Because of the long terminal half-life of the drug, the minimum interval following treatment with ribavirin before pregnancy can be safely initiated is estimated to be 7 months.

Precautions

Because of the reproductive risks associated with ribavirin, its use should be subject to formal risk assessment to protect health care workers and patients alike. Particular attention should be made to the Control of Substances Hazardous to Health (COSHH) regulations. Occupational exposure during nebulisation/aerosol formation limits the acceptance of these methods of delivery.

Drug Interactions

No drug interactions have been identified.

Drug Resistance

No clinical data are available on the development of resistance to ribavirin at present.

Summary

The use of ribavirin is controversial because of the lack of a robust evidence base and safety concerns regarding the potential to cause haemolytic anaemia in the patient and reproductive risks to both patient and health care workers. Ribavirin may be considered where more conventional antiviral therapies have been utilised and the patient is not responding due to possible resistance.
References


(2) Summary of product characteristics for Tamiflu®, electronic Medicines Compendium 2009 [accessed 18 08 09]; Available from: URL: www.medicines.org.uk

(3) HPA, RCA, ICS, ICNARC. Pandemic H1N1 2009 Clinical Practice Note – Managing critically ill cases. HPA website 2009 [accessed 19 09 09]; Available from: URL: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1248854036293


