

Ribavirin Nebulisation Guidance Document

Guidance for the preparation, administration and safety considerations of nebulised ribavirin using the Aiolos nebuliser

This document was compiled by a multidisciplinary team of healthcare professionals from hospitals across the UK

Lorraine Donovan

Team Leader Haematology, University Hospital of Wales

Michaela Fairest

Clinical Procurement Specialist, Sheffield Teaching Hospitals NHS Trust

Leona Graves

Deputy Clinical Governance Coordinator in specialised cancer medicine and rehabilitation, Sheffield Teaching Hospital NHS Trust

Noreen Lewis

Haematology Lead Nurse, University Hospital of Wales

Suzanne Liebersbach

Senior Sister Haematology and Transplant, St James Hospital, Leeds

Sarah O'Connell

Ward Sister Haematology, University Hospitals Leicester

Rachel O'Donnell

Lead Pharmacist, BMT Unit, Bristol Royal Hospital for Children

Louise Parrack

Cardiothoracic Transplant Pharmacist, Papworth Hospital NHS Foundation Trust

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1. Preface

The purpose of this document is to act as a reference material for healthcare professionals who are being trained in the preparation and administration of the drug ribavirin by nebulisation. It is also intended as a reference for those who are deemed to have been competently trained. There has been a demand for a document such as this to provide information on the use and environmental exposure to nebulised ribavirin.

The document was put together by a multidisciplinary team (MDT), which included healthcare professionals from hospitals across the United Kingdom. Personnel involved are listed in the Acknowledgements section.

Ribavirin is a broad-spectrum antiviral agent, which inhibits a wide range of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) viruses by disrupting viral protein synthesis.

The current licensed Virazole[®] (ribavirin for inhalation) dose is 6 g given via a nebuliser at a dose of 20 mg/ml over a 12–18 period (1). However, the most widely used treatment regimen is 6 g given via nebulisation at a dose of 60 mg/mL given in three sessions of 2 hours and has been described in the literature (2). This is more convenient for patients and for hospitals in terms of ward management. This document does not aim to recommend a particular dosing regimen and the chosen regimen should rely on clinical judgment. However, this method of administration has shown to be efficacious and preferable to both patients and staff.

2. Clinical indications

Nebulised ribavirin is indicated for the treatment of patients who have proven viral infection of respiratory syncytial virus (RSV). It has also been widely used for para-influenza virus (3, 4, 5) cultured from nasopharyngeal aspirate (NPA) or bronchoalveolar lavage (BAL), according to local procedures (or via high throat swab if NPA is not practical), in conditions such as:

1. Allogenic or matched unrelated donor (MUD) transplant recipients
2. Autograph patients less than 6 months post transplant
3. Patients with chronic lymphocytic leukaemia (CLL) who have received alemtuzumab (Campath[®]) within the previous 12 months
4. Patients with acute lymphoblastic leukaemia (ALL), acute myelogenous leukaemia (AML), high grade non-Hodgkin's lymphoma (NHL) who are on chemotherapy and neutropenic
5. Patients with myeloma with evidence of lower respiratory involvement
6. Lung transplant patients (single and double)

However, clinical uses are not necessarily limited to the above list. For the current licensed indications please refer to the summary of product characteristics (SPC) located in appendix 4. Details of publications supporting the use of nebulised ribavirin in particular indications are given in appendix 3.

2.1 Other points to consider

The senior nurse on the ward must perform a risk assessment of the patient and the environment before treatment with nebulised ribavirin commences. If any of the MDT have reasonable cause for concern (see examples below) then a decision may be taken to use an alternative formulation of ribavirin. For example:

1. Availability of appropriately trained staff on the ward
2. Patients dependent on high flow oxygen
3. If the patient has uncontrollable diarrhoea, haemorrhagic cystitis, or persistent vomiting
4. Patients who are unable or unwilling to sit for 2 hours with the nebuliser *in situ*

The decision whether to administer nebulised ribavirin or not must be reviewed on a daily basis for each patient by the prescribing consultant and the senior nurse on the ward.

3. Health and safety

3.1 *Exposure to ribavirin*

It is recommended that ribavirin be regarded as a “substance hazardous to health” and therefore the risk of exposure should be reduced to as low a level as is reasonably practicable where use is indicated.

The senior nurse on the ward must perform a risk assessment of the patient and the environment before treatment with nebulised ribavirin starts (see section 2.1).

Staff should be trained in accordance to local trust guidelines to appropriate levels of competency (see section 5).

Systemic exposure to ribavirin may result in the accumulation of the drug in the red blood cells resulting in anaemia after prolonged use (more than 10 days). However, this is more pertinent to long term oral and IV administration and the risk of systemic exposure to ribavirin following nebulisation is low (7, 8).

3.2 *Use by contact lens wearers*

Contact lens wearers should be aware that there have been reports of nebulised ribavirin leaving deposits on contact lenses, which may cause eye irritation. It is strongly recommended that well fitting goggles be worn during the preparation and administration of ribavirin.

3.3 *Staff with asthma and respiratory disorders*

It is recommended that staff known to suffer from asthma or respiratory disorders should avoid entering a patient’s room whilst the nebulised ribavirin is being administered. In addition they should follow safety precautions in section 4.3.

There have been reports of asthma-like symptoms and breathing difficulties in healthcare workers exposed to ribavirin (6, 9). However, these cases are not common and healthcare workers should decrease their risk of exposure by following the procedures in Section 4.

3.4 *Pregnancy*

Oral ribavirin has been shown to be teratogenic in rodents and rabbits (10, 11) but not in primates after oral dosing (12). It is not possible to extrapolate from pregnant animals treated orally to humans exposed to ribavirin aerosol, particularly as there is a marked variability between species in susceptibility to the teratogenic effects of ribavirin (8). Therefore, the teratogenic risk to humans is unknown.

Between January 1994 and December 2007, an estimated 177, 000 patients have been treated with aerosolised ribavirin (13) and the number of health care workers exposed will be a multiple of this number. There have been no reports to suggest a causal relationship between ribavirin aerosol and a birth anomaly in over 10 years of extensive ribavirin use in the USA and Europe.

A pregnancy risk assessment should be undertaken with the ward manager according to trust policy. The option to care for patients should be risk-based for each individual.

Healthcare workers who suspect or know that they are pregnant, planning to conceive, or who are breastfeeding should not prepare or administer ribavirin and should avoid entering a patient’s room whilst the nebulised drug is being administered. In addition they should follow the safety precautions outlined in section 4.

For male health care workers the risk of exposure to nebulised ribavirin is unknown. A study in male rats using IV ribavirin demonstrated alterations in reproductive variables, which were reversible after cessation of ribavirin administration (14). Male health workers should follow the safety procedures outlined in section 4.

4. Methods of reducing exposure

Good hand-washing technique should be maintained at all times. In addition to reducing exposure, the use of protective clothing is good infection control practice.

4.1 *During reconstitution of the drug*

When reconstituting ribavirin, staff must wear appropriate protective, masks (the minimum required is FFP2), disposable apron, gloves, and well fitting goggles. Masks must be worn as per the manufactures recommendations. Masks should be used once.

4.2 *During nebulisation*

For the duration of treatment, all staff entering the patients' room must wear appropriate protective masks, goggles, disposable apron, and gloves. It is not recommended that visitors enter the room during this process.

4.3 *After Nebulisation*

It is recommended that staff and visitors do not enter the room for 45 minutes following administration in a neutral pressure room and 15 minutes in a negative pressure room. If there is a clinical need to enter the room during this period full protective equipment should be worn (see section 4.1).

4.4 *Cleaning after nebulisation*

In the working group's experience, if the drug is administered in a negative pressure room, the amount of ribavirin deposited onto surfaces is minimal.

After each nebulisation, all surfaces should be damp dusted. This is in addition to your normal daily cleaning schedules. Cleaning should be implemented according to you local trust policy. When cleaning the room disposable mask, apron, gloves, and well fitting goggles should be worn.

4.5 *Information for Ward Visitors*

Ideally, nebulised ribavirin should be administered outside visiting hours.

Information notices should be placed on doors before entry to the ward and the doors of patients' rooms. The following wording is suggested: "If you suffer from asthma, wear contact lenses, or are (or planning to become) pregnant, please let the senior nurse know before you enter the patient's room/ward"

Visitors should be advised of the risks of exposure to ribavirin in order that they can make an informed decision whether to stay with the patient or leave.

5. Preparation and administration of nebulised ribavirin

5.1 Preparation of the nebulised ribavirin

Ideally, nebulised ribavirin should be prepared under aseptic conditions in the hospital pharmacy. In hospitals where this service is not available or when the drug needs to be administered out of hours, ribavirin can be reconstituted in the patient's room by a trained member of staff. This is to reduce staff exposure and minimise risk of drug administration errors. It is good practice to reconstitute and administer nebulised ribavirin as a single step procedure.

The following method is given as an example.

1. Required equipment if prepared on the ward:
 - Ribavirin 6 g vial, empty 125 mL infusion bag (or equivalent depending on local practice), and 100 mL water for injection
 - Aiolos nebuliser kit
 - Elephant tubing
 - Baxter Control-A-Flo set or equivalent rate control device
 - Oxygen mask and tubing
 - Drip stand
 - Attention labels for lines and ribavirin solution
2. Required equipment if prepared in pharmacy:
 - Reconstituted ribavirin solution
 - Aiolos nebuliser kit
 - Elephant tubing
 - Baxter Control-A-Flo set or equivalent rate control device
 - Oxygen mask and tubing
 - Drip stand
 - Attention labels for lines and ribavirin solution
3. Practice may vary in accordance with local trust risk assessment policy. Giving a 2-hour nebulisation as an example: the contents of the vial (6 g) should be dissolved in 50 mL of water for injection. When dissolved, this should be transferred into the empty infusion bag. A further 50 mL of water for injection should then be added to the infusion bag (a total of 100 mL) to give a final ribavirin concentration of 60 mg/mL
4. Label the bag clearly with the following text: “**attention nebulisation only**”

5.2 Preparation of Aiolos

There are various ways of delivering the drug to the Aiolos device. Hospital trust approval should be sought as to the method which should be used. It is recommended that graduated oxygen tubing be used, but should comply with clinical governance. The following method is given as an example as demonstrated in the educational DVD.

1. Assemble the Aiolos nebuliser as directed in Appendix 1. Attach the metal clamp to the stand before placing the device within the clamp. **Avoid** attaching to an IV

stand which is being used for IV infusions to ensure that IV and nebulisation equipment is kept separate

2. Connect the oxygen tubing to the lower part of the device (silver coloured connection)
3. Remove the Baxter Control-A-Flo infusion set from its outer wrapping and apply the slide clamp
4. Insert the spike of the Baxter Control-A-Flo set into the polyfusor port of the bag containing the ribavirin solution. Hang the bag on drip stand
5. Turn the dosimeter to prime and then squeeze the drip chamber until it is approximately one third full then prime the line. Apply slide clamp and set the dosimeter to give an approximate flow rate of 17.5 mL/h
6. Attach the end of the Baxter Control-A-Flo infusion set to the luer lock port of the medicine reservoir on the nebuliser and fill approximately to the 2 mL line
7. Connect the elephant tubing (which will deliver the nebulised solution via the mask) to the upper part of the Aiolos device
8. Connect the elephant tubing provided to the upper part at the top of the nebuliser and attach the other end to a face mask
9. Attach the other end to the oxygen or air supply on the ward
10. Release clamp and turn on oxygen supply to 7 L/min

5.3 Cleaning and sterilisation of the Aiolos device

The nebuliser should be cleaned and sterilised before treatment of each new patient according to manufacturer's recommendations, which are given below. However, users should consult with the local infection control team.

1. Cleaning the treatment system: use a heat disinfectant to sterilise ventilator hoses and dry the components in a drying cabinet
2. Cleaning the nebuliser: dismantle the nebuliser into its component parts (nebuliser upper part, insert tube, baffle cap, medicine reservoir, nozzle assembly, and nebuliser lower part). Separate the two parts of the nozzle assembly. Two alternatives for sterilisation of the nebuliser are given below:

Alternative 1 (using disinfection solution)

- According to hospital or clinical procedures, immerse all nebuliser components, apart from hose and nebuliser lower part, in disinfection solution for 30 minutes. The components must be completely immersed in the solution
- Rinse under running water cold water. Place all components in a bowl of clean tap water and leave for approximately 10 minutes
- Clean components using a detergent if necessary and rinse again
- Allow to dry in air
- Wipe over the hose and nebuliser lower part with isopropyl alcohol

Alternative 2 (autoclaving)

- The nebuliser upper part, nozzle assembly, inset tube, medicine reservoir, and baffle cap can be autoclaved (standard autoclave cycles with a maximum temperature of 137°C)
- Disinfect all components before autoclaving

3. Local hospital guidelines should be checked for the disposal of residual medicinal product in the Aiolos nebuliser or tubing
4. To reduce the risk of bacterial contamination, the nebuliser components should not be stored while still damp. Shake off as much water as possible before the components are air dried

6. Training of staff

Training requirements should be included within nurses' personal development plan and documented in their knowledge and skills framework.

A DVD is also available to support educational training of staff and is available from the MEDA Medical department (Medical@medapharma.co.uk).

7. Acknowledgements

Mrs Lorraine Donovan, Team Leader Haematology, University Hospital of Wales.
lorraine.donovan@cardiffandvale.wales.nhs.uk

Michaela Fairest, Clinical Procurement Specialist, Sheffield Teaching Hospitals NHS Trust.
<mailto:michaela.fairest@sth.nhs.uk>

Mrs Leona Graves, Deputy Clinical Governance Coordinator in specialised cancer, Medicine and rehabilitation, Sheffield Teaching Hospital Trust.
Leona.Graves@sth.nhs.uk

Mrs Noreen Lewis, Haematology Lead Nurse, University Hospital of Wales.
noreen.lewis@cardiffandvale.wales.nhs.uk

Miss Suzanne Liebersbach, Senior Sister Haematology and Transplant, St James Hospital, Leeds. Suzanne.liebersbach@leedsth.nhs.uk

Miss Sarah O'Connell, Ward Sister Haematology, University Hospitals Leicester.
sarah.oconnell@uhl-tr.nhs.uk

Miss Rachel O'Donnell, Lead Pharmacist, BMT Unit, Bristol Royal Hospital for Children. Rachel.ODonnell@UHBristol.nhs.uk

Miss Louise Parrack, Cardiothoracic Transplant Pharmacist, Papworth Hospital NHS Foundation Trust louise.parrack@papworth.nhs.uk

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9. Abbreviations and terms

ALL	Acute lymphoblastic leukaemia
AML	Acute myelogenous leukaemia
BAL	Bronchoalveolar lavage
CLL	Chronic lymphocytic leukaemia
DNA	Deoxyribonucleic acid
MDT	Multidisciplinary team
MUD	Matched unrelated donor
NHL	Non-Hodgkin's lymphoma
NPA	Nasopharyngeal aspirate
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
SPC	Summary of product characteristics

Appendix 1: instructions for use of Aiolos nebuliser

Instructions for use

Version 1, 2006-06-09

Art no 10040

CAUTION: Do not assemble or use this device without reading the instructions for use.

This device is not for use at home. Incorrect use of this device can result in failure to deliver the correct dose of medication or damage to equipment.

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1. Introduction

The Aiolos nebuliser for Virazole® (ribavirin) is indicated for administration of Virazole® (ribavirin) aerosol only. Virazole® aerosol is indicated in the treatment of infants and children with severe Respiratory Syncytial Virus (RSV) bronchiolitis. Full details of the indications can be seen in the Virazole Summary of Product Characteristics (SPC).

2. The device

The Aiolos nebuliser for Virazole® consists of:

- Nebuliser for Virazole® (article no 10420)
- Extra upper nebuliser part (article no 10329)
- Instructions for use (article no 10040)

The operation of the Aiolos nebuliser for Virazole® is dependent upon the following equipment and items being provided by the hospital or clinic:

- Aerosol delivery tubing, 60 cm (with plain inside walls) (22 mm diameter) for connecting the upper nebuliser part to a delivery mask, hood or tent. A starter tube will be supplied with the Aiolos nebuliser, however, additional tubes required are to be supplied by the hospital.
- Nebuliser hose (6 mm outer diameter, 4 mm inner diameter) for connecting the nebuliser to the flow meter. In some countries, graduated oxygen tubing may be used instead.
- Compressed air / oxygen source (9–10 L/min). Use air or oxygen that meets specifications for medical breathing use.
- Infusion pump, syringe pump or equivalent device that can be regulated to 17.5 mL/h.
- Infusion bag, syringe or equivalent container containing a solution of ribavirin prepared as per the instructions in the SPC for Virazole® Aerosol.

Further equipment required will depend on the particular chosen mode of aerosol administration. Virazole® aerosol may be delivered to a mask (any mask that allows elephant tubing to be fitted), hood, tent, or mechanical ventilator.

3. Assembly

1. Assemble the nebuliser according to the instructions (see page 6) and connect the nebuliser hose between the nebuliser and the flow meter.
2. Connect the flow meter to the air or oxygen supply.
3. Prepare the Virazole® solution and transfer the solution to the infusion bag. Connect the infusion bag through an infusion pump to the Luer-lock connection on the medicine reservoir (see picture below).
4. Connect the aerosol delivery tubing to the upper nebuliser part.

NOTE:

The length of the aerosol delivery tubing between the Aiolos nebuliser and the hood or tent should be kept as short as conveniently possible to minimise collection of aerosol during operation. The starter delivery tube supplied is 60 cm long. Tubes longer than 90 cm should not be used.

The tubing should be replaced at the same frequency as the wetted parts of the nebuliser. The wet parts of the nebuliser should be cleaned between patients. They should also be cleaned during administration to a patient if crystallisation is observed (see Sections 4.1 and 6).

Note:
Medicine usage rate:
17.5 mL/hour with the
Aiolos Nebuliser for
Virazole® and 3 bar
driving pressure with a
regulator and approx 10
L/min for a flow meter.
The medicine usage rate
may vary somewhat with
different nebulisers and
the rate (mL/hour) may
need to be adjusted
during treatment.



Aerosol delivery
Tubing

Nebuliser

Luer-lock
connection

Nebuliser hose
(driving pressure)

Syringe, infusion
pump or equivalent

5. For use with mask: The aerosol delivery tubing from the Aiolos nebuliser should be connected to the mask.

6. For use with a hood: The aerosol delivery tubing from the Aiolos nebuliser should be placed into the inlet port of the hood.

7. For use with a tent: The tent must be set up with the customary air flow and cooling systems. The aerosol delivery tubing from the Aiolos nebuliser should be connected to the inlet port of the tent.

CAUTION: The Aiolos nebuliser for Virazole® may not cover the patient's total need of air or oxygen delivery.

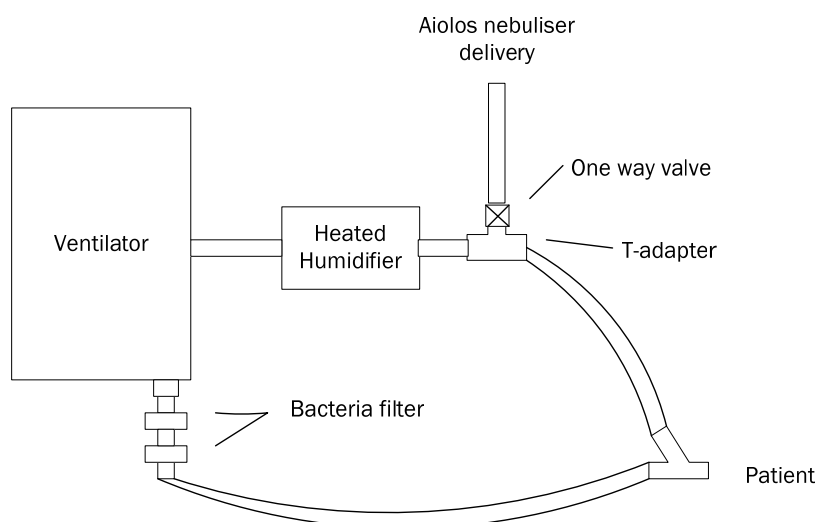
CAUTION: The air/gas source must be connected to the flow meter and turned on whenever the Aiolos nebuliser is in use. The source must have a flow of 9-10 L/min. Use air or oxygen which meets specifications for medical breathing use.

CAUTION: During operation, water/drug collection may form in the medical reservoir cap and in the 22 mm aerosol delivery tubing. Monitor these components hourly. Collection may increase after 4 hours of operation. If excessive collection is seen, these components should be cleaned or replaced.

Before de-activating the Aiolos nebuliser, confirm that the nebuliser has been removed from the patient and the patient has an alternative source of oxygen or air. To de-activate the Aiolos nebuliser, turn off the infusion pump and the flow meter.

8. For use with ventilators: read the instructions for use (below) very carefully.

Connect the Aiolos nebuliser delivery tube into the inspiratory line of the patient breathing circuit immediately downstream from the heated humidifier. Place a one-way valve in the Aiolos nebuliser tubing at the junction with the ventilator circuit (See Figure below). Check the operation of the one-way valve before installing it into the circuit.



CAUTION: Failure to place a one-way valve at the junction of the Aiolos nebuliser tubing line and the inspiratory limb of the ventilator will result in reducing the tidal volume delivery by diverting the ventilator's output through the pressure relief valve.

CAUTION: Virazole® Aerosol may be used for infants requiring assisted ventilation, but requires regular monitoring by experienced hospital personnel. Drug precipitation in the system can be a serious problem. Mechanical ventilators used in conjunction with an Aiolos nebuliser should utilise an internal wire heated ventilator circuit to minimise accumulation of drug precipitate. In addition, bacteria filters in the expiratory limb of the circuit and a high PEEP alarm should be used. A water column relief valve must be employed in circuits with volume-cycled ventilators and may be used as well as in circuits with pressure cycled ventilators.

CAUTION: Water/drug precipitate may form in the one way valve, the ventilation tubing and/or the endotracheal tube; frequent (hourly) monitoring of these components for precipitate is required. If the valve and/or tubing collect precipitate, they must be cleaned or replaced (see Sections 4.1 and 6.).

CAUTION: If airway pressure increases, the endotracheal tube should be checked, and the patient suctioned, to minimise precipitate build-up. Airway pressure increases can also be caused by clogged bacteria filters.

CAUTION: Filters should be changed if an increase in peak inspiratory pressure (PIP) or positive end expiratory pressure (PEEP) of 1-2 cm of water is observed. Because these pressure increases may occur, airway and ventilator circuits should include CONTINUOUS MONITORING.

Use of a pressure monitor with both high and low PEEP alarms is essential to assist the user in detecting changes in the PEEP level.

Water condensation (rainout) associated with the use of conventional tubing may require frequent (hourly) removal of the condensate. To minimise rainout, internal wire-heated tubing must be used.

Maintain the temperature in the circuit at 33-37 °C. It may be necessary to set the heated humidifier at a higher temperature. BEFORE DISCONNECTING the Aiolos nebuliser FROM THE VENTILATOR CIRCUIT, THE TEMPERATURE AT THE HEATED HUMIDIFIER MUST BE ADJUSTED APPROPRIATELY.

CAUTION: Both the heater/humidifier and the internal wire heater sensors must be checked hourly for evidence of water/drug precipitate which can decrease the accuracy of the sensor. When internal wire heated circuits are used, precipitate may also form at the loop of the wire.

4. General operation

1. Connect the flow meter to the gas source.
2. Fill the medicine reservoir with 2-5 mL of the Virazole® solution.
3. Start the flow meter and adjust to give an air flow of 9-10 L/min.
4. Set the infusion pump to give a flow of 17.5 mL/hour (according to the instructions for use for the infusion pump).
5. Start the infusion pump.

The nebuliser will now give a flow rate of 9-10 L per minute.

4.1 Functional checks during use

During treatment with Virazole® the following must be checked:

1. Crystal formation during treatment

During treatment, the medicine solution may form crystal deposits on the inner surfaces of the nebuliser, hoses and connectors and these can affect the flow. It is therefore very important to check the system at regular intervals. Check the system components every hour. In any event it is recommended that the nebuliser is rinsed and the tubing is changed daily.

Procedure for checking crystal formation:

- Turn off the nebuliser and the infusion pump.
- Check for the formation of medicine solution crystals in the nebuliser, all tubing and connectors.
- If the crystal deposit exceeds 1 mm, rinse using sterile water or fit new tubing if necessary.

NB: Local hospital guidelines should be checked for the disposal of residual medicinal product in the Aiolos nebuliser or tubing.

2. Fluid levels during treatment

Check that the fluid level in the medicine reservoir is correct (2-5 mL). The medicine usage rate may vary somewhat with different nebulisers and the rate (mL/hour) may need to be adjusted during treatment.

Other checks

Other monitoring should include normal patient check routines depending on the devices being used.

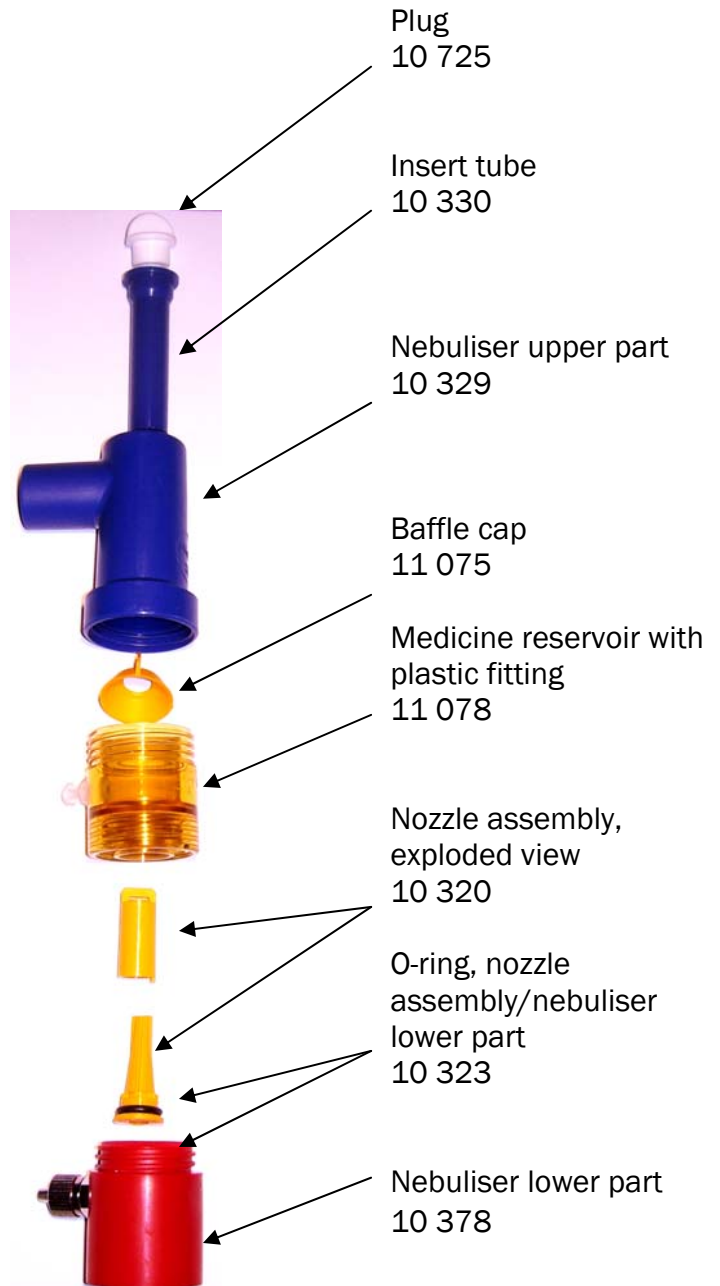
NB: There should be no tension in the tubing. This may occur in the tube to the gas/air supply if this tube is unplugged after the gas/air supply has been started and then the tube is plugged in again without stopping the air supply. There should be no kinks or twists in the tubing.

5. Assembly instructions and spare part list for Aiolos nebuliser for Virazole®

1. Press insert tube down into nebuliser upper part.
2. Press baffle cap firmly into nebuliser upper part.
3. Screw medicine reservoir into nebuliser upper part.
4. Assemble nozzle. The two parts snap together.
5. Check that the black O-ring is properly located.
6. Press the nozzle assembly into the medicine reservoir.
7. Check that the black O-ring is correctly located in the groove of the nebuliser lower part.
8. Screw the nebuliser lower part into the medicine reservoir.

Attachment of hose between nebuliser and driving pressure source:

1. Screw in the hose connector nut on the nebuliser as far as possible
2. Attach the hose.
3. Unscrew the nut so that it locks the hose.
4. Connect the hose to the pressure source in a similar way.



6. Cleaning the Aiolos nebuliser for Virazole®

The nebuliser must be cleaned prior to treatment of each new patient.

6.1 Cleaning the treatment system

Use a heat disinfectant to sterilise ventilator hoses. Dry the components in a drying cabinet.

The nebuliser hose must be changed prior to the treatment of each new patient.

6.2 Cleaning the nebuliser

Dismantle the nebuliser into its component parts, i.e. nebuliser upper part, insert tube, baffle cap, medicine reservoir, nozzle assembly and nebuliser lower part.

Separate the two parts of the nozzle assembly.

Alternative 1. Disinfection solution according to hospital or clinic procedures

Immerse all nebuliser components, apart from hose and nebuliser lower part, in disinfection solution for 30 minutes. The components must be completely immersed in the solution. Then rinse under running cold water. Place all components in a bowl of clean tap water and leave for about 10 minutes. Clean components using a detergent if necessary and rinse again. Allow to dry in air. Wipe over hose and nebuliser lower part with isopropyl alcohol.

Alternative 2. Autoclaving.

The nebuliser upper part, nozzle assembly, inset tube, medicine reservoir and baffle cap can be autoclaved (standard autoclave cycles with a maximum temperature of 137 °C). Disinfect all components before autoclaving.

NB: Local hospital guidelines should be checked for the disposal of residual medicinal product in the Aiolos nebuliser or tubing.

CAUTION: To reduce the risk of bacterial contamination, the nebuliser components should not be stored while still damp. Shake off as much water as possible before the components are air dried.

7. Trouble shooting and maintenance

7.1. Trouble shooting

There is little or no aerosol

- The nebuliser is not correctly assembled.
- The flow meter is turned off, or is not fully adjusted to give a flow rate of 9- 10 L/min.
- The nozzle is dirty or clogged.
- The O-ring on the lower nebuliser part is missing or broken.

The nebuliser is leaking

- Check that the baffle is inserted correctly into the upper nebuliser part
- Check all O-rings, they may be defective or missing.
- Replace O-rings if necessary.

7.2. Maintenance

O-rings should be replaced if necessary as they might dry up after repeated disinfections. The nozzle should be replaced at least every other year.

8. Technical information

Article No. 10040 (Instructions for use)
Class IIa according to MDD (93/42/EEC)



Item Description

Nebuliser: Aiolos nebuliser for Virazole®, Art no 10420
Output flow: 9-10 liters/min

NOTE: Medicine usage rate: 17.5 mL/hour with the Aiolos nebuliser (with baffle cap), Art. No. 10420, and 3.0 bar driving pressure (9-10 L/min). The medicine usage rate may vary somewhat between batches of Aiolos nebulisers and the rate (mL/hour) may need to be adjusted during treatment.

It is recommended that the device is replaced after 2 years of continuous use.

Technical data:

Nebulising pressure: 3.0 bar (9-10 L/min)
Medication output: 0.27 mL/min (3 bar Virazole®)
Mass Median Diameter: 1.7 µm (3 bar Virazole®)

Aiolos Medical AB makes no warranty or representation, either express or implied, with respect to any other manufacturer's items or equipment, their quality, performance, or fitness for a particular purpose. In no event will Aiolos Medical AB be liable for direct, indirect, special, incidental or consequential damages resulting from any defect in construction or performance of other manufacturer's equipment.

Contact information:

Aiolos Medical AB
Fjärrviksvägen 4
653 50 Karlstad
Sweden

Phone: +46 54 53 48 05
Fax: +46 54 53 87 47
E-mail: air@aiolos.se
www.aiolos.se

Appendix 2: suggested items and suppliers

Green oxygen tubing: the oxygen “bubble” tubing from wall oxygen point to nebuliser is available from the NHS supply chain, code FDF352.

Elephant tubing: available from Squadron Medical code 290\7264.

Dosimeter feed tubing: the Control-A-Flo set, IV giving set code is FSB872. Available from the NHS supply chain. Manufactured by Baxter Healthcare. Their code is EMC5908P.

TPN bags: the bags are called ‘Freka Mix’ bags and are from Fresenius Kabi. They are available in 250 mL, 500 mL, 1 L and larger. The reference code for the 250 mL bag is B2860051.

Masks

FFP3 masks are available from Squadron Medical. The code for each mask type is shown in the table below:

Supplier	Code	Description of product
Full Support Healthcare Limited	FSM9	Respirator easimask class FFP3 valved - cone
Full Support Healthcare Limited	FSM9CASE	Respirator easimask class FFP3 valved - cone
Full Support Healthcare Limited	FSM15	Respirator easimask class unvalved - cone
Full Support Healthcare Limited	FSM15CASE	Respirator easimask class FFP3 unvalved - cone

Goggles: available from NHS supply chain. Code BTS002.

Aprons: yellow aprons used for entering infected rooms are available from NHS supply chain code BTB269. White general purpose aprons are also available from NHS supply chain and the code is BTB272.

Gloves: available from Schottlander and are supplied via Squadron Medical. The code depends on the size of the glove:

Extra small: SL877XS

Small: SL877S

Medium: SL877M

Large: SL877L

Extra large: SL877XL

Appendix 3: bibliography

Title

Efficacy of oral ribavirin in lung transplant patients with respiratory syncytial virus lower respiratory tract infection.

Source

The Journal of heart and lung transplantation:theofficial publication of the International Society for Heart Transplantation, {J-Heart-Lung-Transplant},Jan 2009, vol. 28, no. 1, p. 67-71, ISSN: 1557-3117.

Author(s)

Pelaez-Andres, Lyon-G-Marshall,Force-Seth-D,Ramirez-Allan-M, Neujahr-David-C,Foster-Marianne,Naik-Priyumvada-M, Gal-Anthony-A, Mitchell-Patrick-O, Lawrence-E-Clinton.

Author affiliation

Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia 30322, USA.
apelaez@emory.edu.

Abstract

BACKGROUND: Respiratory syncytial virus (RSV) can cause severe lower respiratory tract infection (LRI) and is a risk factor for the development of bronchiolitis obliterans syndrome (BOS) after lung transplantation (LTx). Currently, the most widely used therapy for RSV is inhaled ribavirin. However, this therapy is costly and cumbersome. We investigated the utility of using oral ribavirin for the treatment of RSV infection after LTx. **METHODS:** RSV was identified in nasopharyngeal swabs (NPS) or bronchoalveolar lavage (BAL) using direct fluorescent antibody (DFA) in 5 symptomatic LTx patients diagnosed with LRI. Data were collected from December 2005 and August 2007 and included: age; gender; type of LTx; underlying disease; date of RSV; pulmonary function prior to, during and up to 565 days post- RSV infection; need for mechanical ventilation; concurrent infections; and radiographic features. Patients received oral ribavirin for 10 days with solumedrol (10 to15 mg/kg/day intravenously) for3 days, until repeat NPS were negative. **RESULTS:** Five patients had their RSV-LRI diagnosis made at a median of 300 days post-LTx. Mean forced expiratory volume in 1 second (FEV(1)) fell 21% ($p<0.012$) during infection. After treatment, FEV(1) returned to baseline and was maintained at follow-up of 565 days. There were no complications and no deaths with oral therapy. A 10-day course of oral ribavirin cost \$700 compared with \$14,000 for nebulized ribavirin at 6 g/day. **CONCLUSIONS:** Treatment of RSV after LTx with oral ribavirin and corticosteroids is well tolerated, effective and less costly than inhaled ribavirin. Further studies are needed to directly compare the long-term efficacy of oral vs nebulized therapy for RSV.

Title

Herpes simplex pneumonia: Combination therapy with oral acyclovir and aerosolized ribavirin in an immunocompetent patient.

Source

Current Therapeutic Research - Clinical and Experimental, {Curr-Ther- Res-Clin-Exp}, January 2004, vol.65, no.1, p. 90-96, 23 refs, CODEN: CTCEA, ISSN: 0011-393X.

Author(s)

Terzano-Claudio, Petroianni-Angelo, Ricci-Alberto.

Author affiliation

Dr.C.Terzano: Respiratory Diseases Unit, Dept. of Cardiovasc. And Resp. Sci.,
Fondazione E. Lorillard Spencer C., Rome, Italy. Email: cterzano@tin.it.

Abstract

Background: Herpes simplex viruses (HSVs) are known to cause respiratory tract infections in immunocompromised hosts and, in rare instances, in immunocompetent hosts. Numerous in vitro and in vivo studies have shown that aerosolized administration of ribavirin can potently and selectively inhibit viral replication in pulmonary disease, thereby increasing the effectiveness of acyclovir in HSV.

Objective: In this case study, we reported on a 46-year-old immunocompetent woman with HSV type1 pneumonia with bilateral pulmonary infiltrates but without mucocutaneous lesions. **Methods:** The diagnosis was confirmed using cytology, viral culture, and serology. Because of the persistence of fever and dyspnea, we chose an anti viral therapy. The patient received oral acyclovir and aerosolized ribavirin to improve the antiviral effectiveness of the acyclovir and to reduce the symptoms and the time to resolution of the pulmonary disease. **Results:** After 3 days of therapy, dyspnea and fever decreased and hypoxemia improved. After 2 weeks, computed tomography showed complete resolution of pulmonary abnormalities. The patient did not report any adverse effects. **Conclusions:** In our case study, we demonstrated that therapy with a combination of aerosolized ribavirin and oral acyclovir may be useful to reduce the severity of viral infection, the adverse effects, and the days of hospitalization. To our knowledge, this is the first report in the literature of the synergistic effects of the combination of aerosolized ribavirin and oral acyclovir in the treatment of an immunocompetent patient with HSV pneumonia.

Title

Long-term therapy with aerosolized ribavirin for parainfluenza 3 virus respiratory tract infection in an infant with severe combined immunodeficiency.

Source

Pediatric transplantation, {Pediatr-Transplant}, Mar 2007, vol. 11, no. 2, p. 209-13, ISSN: 1397-3142.

Author(s)

Stankova-Jitka, Carret-Anne-Sophie, Moore-Dorothy, McCusker-Christine, Mitchell-David, Davis-Michael, Mazer-Bruce, Jabado-Nada.

Author affiliation

Division of Hematology and Oncology, Montreal Children's Hospital, McGill University Health Centre, Montreal, QC, Canada.

Abstract

We report the case of an infant with severe combined immunodeficiency who was presented with PIV3 infection. Aerosolized ribavirin was administered for 10 months until the child gained a functional immune system through an allogeneic hematopoietic stem cell transplant and cleared PIV3 infection. No adverse effect was observed in the child and in healthcare personnel, with a follow-up of three years. Despite the burden of aerosolized administration, early and prolonged administration of aerosolized ribavirin was feasible, well tolerated, and safe for the patient and the caregivers. This is a case report and no definite conclusions can be drawn. However, our experience suggests that prolonged aerosolized ribavirin administration should be considered for the treatment of PIV3 infection in the context of primary

immunodeficiency, where there is no currently available treatment, until a functional immune system is gained.

Title

Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respirator tract infection in hematopoietic cell transplant recipients.

Source

Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, {Clin-Infect-Dis}, 15 Jan 2007 (epub: 05 Dec 2006), vol. 44, no. 2, p. 245-9, ISSN: 1537-6591.

Author(s)

Boeckh-Michael, Englund-Janet, Li-Yufeng, Miller-Carole, Cross-Alan, Fernandez-Humberto, Kuypers-Jane, Kim-Hyung, Gnann-John, Whitley-Richard.

Author affiliation

Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.
mboeckh@FHCRC.org.

Abstract

BACKGROUND: Respiratory syncytial virus infection of the upper airways may progress to fatal pneumonia in hematopoietic cell transplant recipients. The safety and efficacy of aerosolized ribavirin in preventing disease progression is unknown. **METHODS:** In a multicenter prospective trial, hematopoietic cell transplant recipients with respiratory syncytial virus infection of the upper airways were randomized to receive ribavirin (2 g 3 times daily) or supportive care for 10 days. The primary end point was progression to radiographically proven pneumonia. Secondary endpoints included virologically proven respiratory syncytial virus pneumonia, viral load changes, and safety. **RESULTS:** Fourteen patients were randomized to 1 of 2 treatment arms. The trial was discontinued after 5 years because of slow accrual. Pneumonia at 1 month after randomization occurred in 1 of 9 patients who received ribavirin and in 2 of 5 patients who received supportive care ($P=.51$); virologically proven respiratory syncytial virus pneumonia occurred in 0 of 9 and 2 of 5 patients, respectively ($P=.11$). At 10 days after randomization, the average viral load decreased by 0.75 log₁₀ copies/mL in ribavirin recipients, compared with a viral load increase of 1.26 log₁₀ copies /mL in untreated patients ($P=.07$). No discontinuations of ribavirin therapy because of adverse effects occurred during 84 drug administrations. Rates of adverse events were similar in both groups. **CONCLUSIONS:** Preemptive aerosolized ribavirin treatment appeared to be safe, and trends of decreasing viral load over time were observed. However, proof of efficacy remains elusive in hematopoietic cell transplant recipients.

Title

Aerosolized ribavirin-induced reversible hepatotoxicity in a hematopoietic stem cell transplant recipient with Hodgkin lymphoma.

Source

Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, {Clin-Infect-Dis}, 15 Apr 2006 (epub: 13 Mar 2006), vol. 42, no. 8, p. e72-5, ISSN: 1537-6591.

Author(s)

Chaves-Jorge, Huen-Auris, Bueso-Ramos-Carlos, Safdar-Amar, Vadhan- Raj-Saroj.

Author affiliation

Department of Lymphoma and Myeloma, Section of Cytokines and Supportive Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA.

Abstract

We describe a case of acute hepatic toxicity associated with aerosolized ribavirin in a bone marrow transplant recipient with documented respiratory syncytial virus infection. The temporal relationship with drug administration and the liver biopsy results suggested drug-induced hepatic injury. As the use of aerosolized ribavirin to treat respiratory syncytial virus infections continues, it is imperative that careful attention be paid to possible adverse effects of therapy in the high-risk population of immunosuppressed patients.

Title

Clinical features and outcomes of paramyxoviral infection in lung transplant recipients treated with ribavirin.

Source

The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation, {J-Heart-Lung-Transplant}, Jul 2003, vol. 22, no. 7, p. 745-53, ISSN: 1053-2498.

Author(s)

McCurdy-Lewis-H, Milstone-Aaron, Dummer-Stephen.

Author affiliation

Infectious Diseases, Vanderbilt Transplant Center, Vanderbilt University School of Medicine, Nashville, Tennessee 37027, USA.

Abstract

BACKGROUND: Paramyxoviral infections are reported in 6% to 21% of lung transplant recipients. Aerosolized ribavirin is used to treat paramyxoviral infections, but data on outcomes of this treatment in lung transplant patients are limited. **METHODS:** Lung recipients treated with aerosolized ribavirin from 1992 through 2000 for pulmonary respiratory syncytial virus (RSV) or parainfluenza virus (PIV) infection were assessed for the following variables: age; gender; underlying diagnosis; time from transplantation; duration of illness; clinical symptoms; and change from baseline FEV(1) (forced expiratory volume in 1 second). Outcomes included FEV(1) values at 30 and 90 days, need for intubation, development of acute rejection or obliterative bronchiolitis (OB) in the year after treatment; and 90-day and overall mortality. **RESULTS:** Fifteen patients received ribavirin for a median of 5 days (range 3 to 7) for 17 episodes of RSV (n = 12) or PIV (n = 5) infection. The clinical presentations of RSV and PIV infection were similar. Infection occurred a median of 520 days (range 7 to 1700) after transplantation. Three episodes required intubation; 2 episodes were fatal accounting for a 90-day mortality per episode of 12%. The FEV(1) at presentation declined by 25% (range 4% to 44%) from baseline. In 3 patients the FEV(1) did not return to baseline by 90 days or thereafter. All 3 patients had underlying pulmonary fibrosis (IPF) vs no IPF in 0 of 9 evaluable patients who recovered (p = 0.009). There was no correlation between response to ribavirin and subsequent development of OB. **CONCLUSIONS:** About 33% of lung transplant patients with lower respiratory tract paramyxoviral infections who were treated with inhaled ribavirin died or did not return to baseline FEV(1). This effect was acute and not associated with later complications, including OB. Underlying IPF may be a risk factor for failure to return to baseline. Larger, prospective, multicenter studies are required to confirm these findings.

Title

Preemptive treatment of pediatric bone marrow transplant patients with a symptomatic respiratory syncytial virus infection with aerosolized ribavirin.

Source

Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, {Biol-Blood-Marrow-Transplant}, 2001, vol. 7 Suppl, p. 16S-18S, ISSN: 1083-8791.

Author(s)

Adams-R-H.

Author affiliation

Pediatric Blood and Marrow Transplant, University of Utah/Primary Children's Medical Center, Salt Lake City 84132, USA. roberta.adams@hsc.utah.edu.

Abstract

Respiratory syncytial virus (RSV) is a cause of serious respiratory infections in pediatric patients. RSV infection may be especially devastating in pediatric bone marrow transplant (BMT) recipients. Because of the high mortality attributed to RSV lower respiratory tract infection, a pilot study of preemptive treatment of asymptomatic RSV shedding in pediatric BMT recipients was conducted. Nasopharyngeal wash specimens from 25 pediatric BMT recipients were screened for RSV infection prior to patients' admission to the University of Utah Pediatric Bone Marrow Transplant Unit and then on a weekly basis during the 1996 and 1997 RSV seasons. Samples from 7 asymptomatic patients tested positive for RSV, and the patients were treated with aerosolized ribavirin for 5 days; none developed clinical RSV disease. Two patients had multiple episodes asymptomatic RSV shedding. One patient required 2 courses of treatment for clearance of RSV.

Title

Respiratory syncytial virus upper respiratory tract illnesses in adult blood and marrow transplant recipients: combination therapy with aerosolized ribavirin and intravenous immunoglobulin.

Source

Bone marrow transplantation, {Bone-Marrow-Transplant}, Apr 2000, vol. 25, no. 7, p. 751-5, ISSN: 0268-3369.

Author(s)

Ghosh-S, Champlin-R-E, Englund-J, Giralt-S-A, Rolston-K, Raad-I, Jacobson-K, Neumann-J, Ippoliti-C, Mallik-S, Whimbey-E.

Author affiliation

Department of Medical Specialties, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.

Abstract

Respiratory syncytial virus (RSV) is an important cause of serious respiratory illness in blood and marrow transplant (BMT) recipients. In some subsets of these immunocompromised patients, RSV upper respiratory illnesses frequently progress to fatal viral pneumonia. The frequency of progression to pneumonia is higher during the pre- engraftment than during the post-engraftment period. Once pneumonia develops, the overall mortality is 60-80%, regardless of the treatment strategy. We performed a pilot trial of therapy of RSV upper respiratory illnesses using aerosolized ribavirin and IVIG (500 mg/kg every other day), with the goal of preventing progression to pneumonia and death. Two dosages of ribavirin were used: a

conventional regimen (6 g/day at 20 mg/ml for 18 h/day) and a high- dose short-duration regimen (6 g/day at 60 mg/ml for 2 h every 8 h). Fourteen patients were treated for a mean of 13 days (range: 7-23 days). In 10 (71%) patients, the upper respiratory illness resolved. The other four (29%) patients, three of whom were in the pre- engraftment period, developed pneumonia, which was fatal in two. The most common adverse effect was psychological distress at being isolated within a scavenging tent. In conclusion, prompt therapy of RSV upper respiratory illnesses in BMT recipients with a combination of aerosolized ribavirin and IVIG was a safe and promising approach to prevent progression to pneumonia and death.

Title

High-dose, short-duration ribavirin aerosol therapy compared with standard ribavirin therapy in children with suspected respiratory syncytial virus infection.

Source

Journal of Pediatrics. 1994, vol. 125, no. 4, p. 635–41.

Author(s)

Englund JA, Piedra PA, Ahn YM, Gilbert BE, Hiatt P.

Author affiliation

Department of Microbiology and Immunology, Baylor College of Medicine, Houston, Texas 77030.

Abstract

Children with suspected respiratory syncytial virus infection were examined prospectively in a randomized evaluation of standard ribavirin aerosol therapy (6 gm/300 ml water for 18 hours daily) compared with high-dose, short-duration ribavirin aerosol therapy (6 gm/100 ml water given for a period of 2 hours three times a day) by means of an oxygen hood (n = 20) or a ventilator (n = 12). Viral shedding was quantitated daily; clinical observations were recorded daily by 2 physicians aware and one unaware of treatment assignments. Study characteristics evaluated at entry were not significantly different in the high-dose and the standard-dose groups. Viral titers and clinical scores decreased similarly in both groups during the study; pulmonary function test results were also similar at discharge in children not receiving mechanical ventilation. Potential complications related to aerosol therapy were noted in three patients (one hood patient who was receiving standard therapy; two patients with an endotracheal tube in place who were receiving high-dose therapy); substantial crystallization was noted in the tubing of the patients undergoing intubation and receiving high-dose therapy. Environmental sampling revealed that ribavirin was nearly undetectable near patients supported by mechanical ventilation who were receiving either form of therapy, and was significantly decreased on a daily basis in patients without an endotracheal tube who were receiving high-dose therapy compared with those receiving standard therapy. The effects of high-dose, short-duration aerosol ribavirin therapy were similar to those of standard-dose therapy in our study patients and resulted in a decreased release of ribavirin into the room of patients receiving therapy by means of an oxygen hood.

Title

Pre-emptive oral ribavirin therapy of paramyxovirus infections after haematopoietic stem cell transplantation: a pilot study.

Source

Bone Marrow Transplantation. 2001, vol. 28, no8, p. 759–763.

Author(s)

Chakrabarti S, Collingham KE, Holder K, Fegan CD, Osman H, Milligan DW.

Author affiliation

Department of Haematology, Birmingham Heartlands Hospital, Birmingham, UK.

Abstract

Infections with the paramyxoviruses, respiratory syncytial virus (RSV) and parainfluenza virus (PIV) can result in serious morbidity and mortality after haemopoietic stem cell transplant (HSCT). Once pneumonia develops, the outcome of these infections is often poor despite anti-viral therapy. Aerosolised ribavirin has been evaluated as pre-emptive therapy for post-transplant RSV infections with some success. Due to the financial and logistic burden involved with the use of aerosolised ribavirin, we explored the efficacy and toxicity of oral ribavirin for pre-emptive therapy of post-transplant RSV and PIV infections in a dose escalating schedule (15-60 mg/kg/day). Five episodes each of RSV and PIV were treated in seven patients. Five patients were receiving treatment for GVHD and two acquired the infection in the pre-engraftment period. All the episodes of RSV infection improved with oral ribavirin with dose escalation to 30-45 mg/kg in three of them. On the other hand, only two of the five PIV infections improved with oral ribavirin. Of the three non-responders, two infections were acquired in the pre-engraftment period with one death from PIV pneumonia. Reversible anaemia was the only side-effect noted in patients treated for over 2 weeks. Thus, the use of oral ribavirin was well tolerated in the post-transplant period with no untoward toxicities. There was a trend towards better response in RSV infections, which needs to be further explored in controlled studies.

Appendix 4: summary of product characteristics

Meda Pharmaceuticals

Sky Way House, Parsonage Road, Takeley,
Bishop's Stortford, CM22 6PU
Telephone: 0845 460 0000
Fax: 0845 460 0002
Medical Information Direct Line: +44 (0)1748 828 810
Medical Information e-mail:
meda@professionalinformation.co.uk
Medical Information Fax: +44 (0)1748 828 801



Summary of Product Characteristics last updated on the eMC: 21/03/2005

Virazole Aerosol**1. NAME OF THE MEDICINAL PRODUCT**

Virazole (Ribavirin) Aerosol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ribavirin 6 g

International non-proprietary name (INN): Ribavirin

Chemical Name: 1-Beta-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide

3. PHARMACEUTICAL FORM

Powder for inhalation solution.

4. CLINICAL PARTICULARS**4.1 Therapeutic indications**

Virazole is indicated in the treatment of infants and children with severe respiratory syncytial virus (RSV) bronchiolitis.

Important: Ribavirin aerosol is more effective when instituted within the first 3 days of the treatment of bronchiolitis. Treatment early in the course of the disease may be necessary to achieve efficacy.

Treatment with Virazole must be accompanied by, and does not replace, standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

Nebulised bronchodilators, when clinically indicated, should be administered with the small particle aerosol

generator (SPAG) generator or Aiolos nebuliser turned off.

4.2 Posology and method of administration

Ribavirin aerosol is only recommended for use in infants and children.

Aerosol administration or nebulisation should be carried out in a SPAG or Aiolos nebuliser. Before use read the relevant Operator's Manual for instructions.

Treatment is carried out for 12 to 18 hours per day for at least 3 and no more than 7 days and is part of a total treatment programme.

The daily dose is prepared by dissolving 6 g of ribavirin in a minimum of 75 ml Water for Injection BP. Shake well. Transfer dissolved drug and dilute to a total volume of 300 ml of Water for Injection BP to give a 20 mg/ml ribavirin solution.

In the SPAG unit and Aiolos nebuliser the average concentration for a 7 hour period is 190 µg/l of air.

Method of administration

Please see point 6.6 for instructions on preparation of the aerosol solution.

The aerosol is delivered to an infant oxygen hood from the SPAG aerosol generator or Aiolos nebuliser. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see Operator's Manual). However, the volume of distribution and condensation area are larger in a tent and the efficacy of this method of administration has been evaluated only in a small number of patients.

4.3 Contraindications

Ribavirin is contra-indicated in females who are or may become pregnant and it should be noted that ribavirin can be detected in human blood even four weeks after oral administration has ceased.

4.4 Special warnings and precautions for use

Precipitation of the drug in respiratory equipment and consequent accumulation of fluid in the tubing has caused difficulties for patients requiring assisted ventilation.

In infants requiring assisted ventilation, Virazole should only be used when there is constant monitoring of both patients and equipment.

Directions for use during assisted ventilation are given in the SPAG or Aiolos manual, which should be read carefully before such administration.

Occupational exposure

Nebulised Virazole may potentially escape into the hospital environment during therapy. However, ribavirin was not detected in the erythrocytes, plasma or urine of subjects exposed for a mean of 25 hours during 5 consecutive days. Reports of occupational asthma have been reported rarely although the causal link to ribavirin is unknown since respiratory viruses may induce reactive airways disease in addition to other symptoms including headache, fever, nasal congestion and wheezing. However, care should be exercised, particularly in healthcare workers with pre-existing reactive airways diseases.

Health care workers directly providing care to patients receiving aerosolised Virazole should be aware that ribavirin has been shown to be teratogenic in rabbits and rodents but not in baboons. However, no reports of teratogenicity in the offspring of mothers who were exposed to Virazole aerosol during pregnancy have been confirmed and the teratogenic risk of Virazole to humans is unknown. As a precaution, women who are pregnant or trying to become pregnant should avoid exposure to the Virazole aerosol.

It is good practice to avoid unnecessary occupational exposure to chemicals whenever possible. Several methods have been employed to lower environmental exposure during Virazole use. The most practical of these is to turn the SPAG or Aiolos Nebuliser off for 5 to 10 minutes prior to prolonged contact.

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Pregnancy and lactation

Ribavirin is contra-indicated in females who are or may become pregnant, and in nursing mothers. Ribavirin can

be detected in human blood four weeks after administration has ceased. Although there are no pertinent human data, oral ribavirin has been found to be teratogenic in tested rodent species. Pregnant baboons given up to 120 mg/kg/day orally over a 4 week period and within 20 days of gestation failed to exhibit any teratogenic effects.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Side-effects: Several serious adverse events occurred in severely ill infants with life-threatening underlying disease, many of whom required assisted ventilation. These events included worsening of respiratory status, bacterial pneumonia and pneumothorax. The role of ribavirin aerosol in these events has not been determined.

Anaemia (often of a haemolytic variety) and reticulocytosis have been reported with oral and intravenous administration. Rarely, cases of non-specific anaemia and haemolysis have been reported spontaneously in association with the aerosol administration of Virazole.

4.9 Overdose

No overdoses have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ribavirin has anti-viral inhibitory activity in vitro against respiratory syncytial virus, influenzae virus and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus in experimentally infected cotton rats.

The inhibitory activity of ribavirin on RSV in cell cultures is selective. The mechanism of action is unknown, but there is evidence that ribavirin interferes with protein translation by mRNA of several other RNA viruses, possibly the result of interference with formation of the 5' cap structure of mRNA.

5.2 Pharmacokinetic properties

Assay for ribavirin in human materials is by a

radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four paediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day had plasma concentrations ranging from 0.44 to 1.44 μM , with a mean concentration of 0.76 μM . The plasma half-life was reported to be 9.5 hours. Three paediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 μM , with a mean concentration of 6.8 μM .

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue cultures by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

5.3 Preclinical safety data

Pertinent information is included in the Pregnancy and Lactation section.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable.

6.2 Incompatibilities

None known.

6.3 Shelf life

5 years. After reconstitution in Water for Injections, Virazole should be used within 24 hours.

6.4 Special precautions for storage

Store in a dry place. Store below 25°C.

6.5 Nature and contents of container

100 ml Type 1 glass serum bottle with butyl rubber closure and aluminium seal with tear-off septum. Each bottle contains 6 g ribavirin as a lyophilised white cake. Virazole is packaged in cartons of three bottles.

6.6 Special precautions for disposal and other handling

By aseptic technique dissolve the powder in a minimum of 75 ml Water for Injections BP in the 100 ml vial. The solution should be adequately mixed to ensure complete dissolution. Shake well. It is not recommended that this solution is heated during dissolution. When using the SPAG generator, transfer the solution to the clean, sterilised 500 ml flask and dilute to a final volume of 300 ml with Water for Injections BP. When using the Aiolos nebuliser, transfer the solution into an infusion bag and dilute to a final volume of 300 ml with Water for Injections BP. The final concentration should be 20 mg/ml.

The Water for Injections BP used to make up the Virazole solution should not have any antimicrobial agent or any other substance added and all solutions should be inspected for particulate matter and discoloration prior to administration.

See guidelines for avoiding unwanted exposure to Virazole aerosol under 4.4. Special warnings and special precautions for use.

7. MARKETING AUTHORISATION HOLDER

Valeant Pharmaceuticals Ltd

Cedarwood

Chineham Business Park

Crockford Lane

Basingstoke

Hampshire RG24 8WD

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