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Respiratory Care Department – Sample Protocol

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Background Information

Indications and Usage

The use of the nebulized antimicrobial agent, pentamidine isethionate, is currently thought to be somewhat effective for the prophylaxis of *Pneumocystis carinii* pneumonia (PCP) in cancer patients who are receiving chemotherapy that may result in immunosuppression. Historically, nebulized pentamidine was widely used in the mid-1980s to mid-1990s for both treatment and prophylaxis of PCP in HIV positive patients with and without full-blown AIDS. However, it has largely fallen out of use on HIV patients in favor of a variety of other pharmaceutical regimens. Nevertheless, its use in possibly preventing PCP in intentionally immunosuppressed patients is a contemporary reality for both adults and children.

Accordingly, it is important to administer the drug properly, so as to allow the greatest possible amount of drug to be inhaled and distributed and deposited in endobronchial regions of the lung. It is likewise important that respiratory therapists and other caregivers be protected from breathing collateral aerosol consisting of nebulized pentamidine particles. This is best accomplished by using a high-efficiency delivery system with integral exhalation filtration to avoid leakage of pentamidine aerosol into the ambient environment.

Although improvements in nebulization equipment over the original Respirgard II nebulizer have been accomplished, many institutions will elect to use isolation chambers or hoods and/or negative pressure rooms during nebulized pentamidine administration. This is appropriate to protect against drug particles and pathogenic organisms that may be forcibly exhaled as breathable droplets during coughing.

Because PCP occurs primarily at the alveolar level, a nebulizer capable of generating particles of less than 2 μ M (MMAD) is required. Further, a substantial output (Inhaled Mass) is required. Inhaled Mass should equal or exceed that of the Respirgard II nebulizer, which was the device originally described for nebulized pentamidine in 1989¹.

Pharmacology and Pharmacokinetics

Pentamidine isethionate is a member of a class of compounds known as aromatic diamidines. The precise mechanism of antiprotozoal action of pentamidine isethionate has not been fully elucidated. Several mechanisms of action have been suggested including inhibition of DNA, RNA, phospholipid and protein synthesis, but the relative role of each mechanism to the overall antiprotozoal activity may vary for different types of protozoa. In vitro, pentamidine appears to have a direct cidal effect on *P. carinii* although the drug only moderately inhibits glucose metabolism, protein synthesis, RNA synthesis and intracellular amino acid transport.

Following administration of a single 4 mg/kg i.m. or i.v. dose of pentamidine isethionate in humans, peak plasma concentrations averaged 209 ng/mL approximately 40 minutes after the i.m. dose and 612 ng/mL

after completion of a 2-hour infusion. Following daily i.m. or i.v. doses of 4 mg/kg, there appeared to be little variation in plasma concentrations from day to day and little increase with successive doses, although one study found increased trough concentrations and drug accumulation with multiple dosing.

Following oral inhalation of pentamidine isethionate via nebulization, broncho-alveolar concentrations of the drug were substantially higher than those attained following a comparable i.v. dose, while plasma concentrations were substantially lower; pentamidine appears to undergo limited absorption from the respiratory tract into the systemic circulation. Pentamidine appears to be extensively distributed and/or bound to body tissues. Following i.m. and i.v. administration of a single 4 mg/kg dose in patients with a normal kidney function, plasma concentrations declined in a biphasic manner with terminal elimination half-lives of 9.4 and 6.4 hours, respectively.

After repeated i.m. administration for 10 to 12 days, approximately 15% to 20% of the daily dose was recovered in the urine, apparently as unchanged drug. Pentamidine appears to be eliminated very slowly from tissues in which it accumulates (i.e. liver, lungs) and decreasing amounts of the drug could be detected in the urine for 6 to 8 weeks after cessation of therapy.

The extent of pentamidine distribution and accumulation following chronic inhalation therapy is not known.

In a series of patients treated for *P. carinii* pneumonia, the highest plasma pentamidine concentrations were found in those with elevated BUN levels. Since the major route of elimination is renal, the activity of pentamidine should be anticipated to be prolonged in the presence of severe renal function impairment. No pharmacokinetic data are available following oral inhalation of pentamidine in patients with impaired hepatic or renal function.

Warnings

The most common side effects of nebulized pentamidine are coughing and a sensation of tightness in the chest. These side effects are usually relieved or prevented by pretreatment with nebulized albuterol. Other side effects may include fatigue, shortness of breath, dizziness, nausea and a metallic taste in the mouth. Side effects may be more pronounced if: (a) a high efficiency nebulizer system is used or (b) the patient is also receiving pentamidine by the parenteral route.

Precautions

If possible, patients should be screened for active tuberculosis before starting aerosolized pentamidine therapy to avoid the unnecessary exposure of others. Droplet precautions should be taken with HIV and Tb patients so that caregivers avoid inhalation of airborne droplets expectorated by the patient during coughing. Additional engineering controls are typically used to strengthen the effectiveness of droplet precautions. These controls include filtered exhalation port on aerosol delivery system, treatment of the patient in a hood, chamber or negative pressure room and use of appropriate personal protective equipment (e.g. N-95 respirator) by caregivers.

Pretreatment with inhaled bronchodilators minimizes cough and bronchospasm.

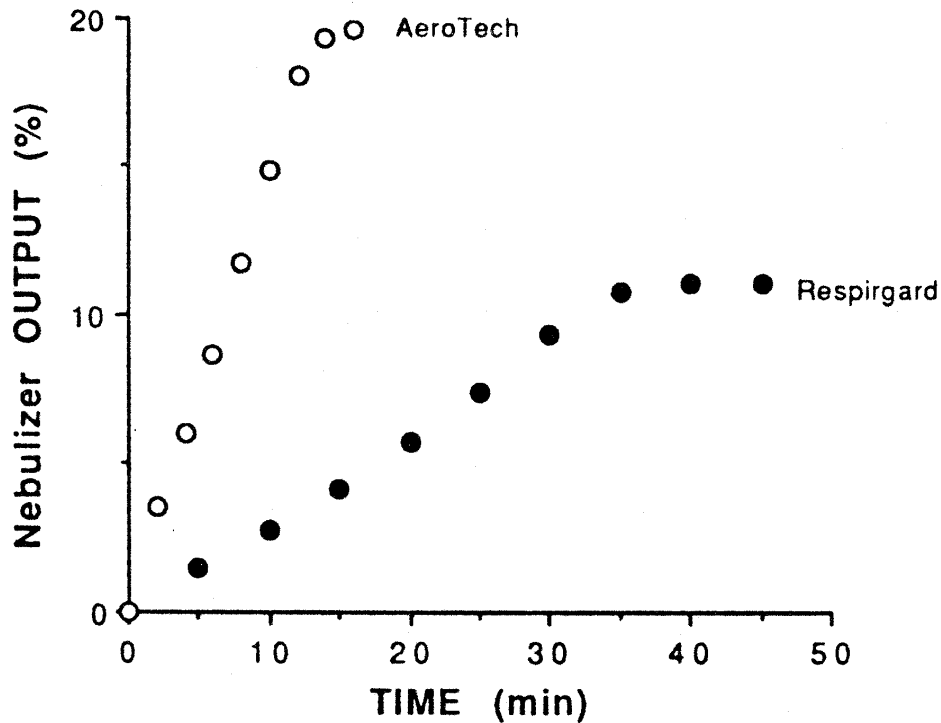
The medicine comes as a lyophilized powder that needs to be mixed with sterile water before it is given. The powder can be kept at room temperature away from heat, moisture, or light. After the powder is mixed with sterile water, you can keep it at room temperature for 2 days (48 hours). Keep the medicine out of direct light. If unused after 2 days, discard the mixed medication.

Dosage

For the purposes of this protocol, the term “prescribed dose” will mean the amount of drug that is prescribed by the ordering physician to be placed in the nebulizer. However, due to the well-known inefficiencies of nebulizer systems, it should be understood and appreciated that the dose placed in the nebulizer is not the “dose” that the patient actually receives (inhales). This can be confusing but is a fact of life with respect to the delivery of aerosolized medications by nebulizer systems. The inhaled dose is best described by the term “inhaled mass,” which is that fraction of the dose placed in the nebulizer that is inhaled².

Typically, for treatment of active PCP in HIV patients, a “prescribed dose” of 300 mg of pentamidine is administered by nebulizer once or twice daily. For PCP prophylaxis, a “prescribed dose” of 150 – 300 mg of pentamidine is administered by nebulizer once or twice a month (i.e. once every 2 to 4 weeks). However, these are not hard and fast rules and variation in prescribing can be expected.

The inhaled dose or “inhaled mass” is dependent upon the performance of the nebulizer system and the patient’s breathing pattern (rate, depth, inspiratory time fraction). The first widely used nebulizer for pentamidine was the Marquest Respirgard II, which was described in the literature by Montgomery^{1,3}. Other nebulizers, the performance of which have been demonstrated to be equivalent to, or better than, the Respirgard II have been used in place of the Respirgard II. The Healthline Medicator+Plus High-Efficiency Aerosol Drug Delivery System is our recommended alternate system. Subsequent investigators determined that the Respirgard II was actually a very **inefficient** nebulizer and, although it had a suitable particle size (MMAD < 2.0 μ M), the amount of drug delivery was low and the amount of time necessary to achieve drug delivery was extremely prolonged (~30 minutes)⁴. These factors obviously mitigate against effective nebulization therapy. In fact, the following plot of inhaled mass against time⁴, for the Marquest Respirgard II and another nebulizer show how slow and inefficient the Respirgard II actually is:



Aerosol Delivery with the low-efficiency Respirgard II:

From the inhaled mass/time graph above, it can be seen that the Respigard II device achieves about an 11% inhaled mass in approximately 35-40 minutes. Accordingly, the delivered mass of pentamidine from a prescribed dose of 300 mg placed in the nebulizer would be 33 mg, provided that the patient was able to tolerate and receive the entire 35-40 minute treatment. Many patients fatigue quickly while receiving aerosol therapy and end the treatment prematurely, thereby receiving even less inhaled medication.

Recommended Delivery System: Healthline Medicator®+Plus “Aerosol Maximizer”

Typical inexpensive hospital nebulizers designed to administer bronchodilators are not appropriate for nebulized pentamidine therapy because they are inefficient, target upper and central airways rather than peripheral airways, take too long to administer the entire dose and some lack exhalation port filtration that protects healthcare workers from occupational exposure to the exhausted aerosol. Merely placing a filter over the exhalation port does not transform the typical hospital nebulizer into an effective delivery system for pentamidine. Although the Respigard II has an exhalation filter and creates drug particles in the appropriate size range, it exhibits the other deficiencies of standard nebulizers. Therefore, this protocol specifies the “Medicator® Plus Aerosol Maximizer,” Cat # AM-602, a high efficiency aerosol drug delivery system, specifically designed for targeted delivery of special-purpose drugs to endobronchial areas while protecting the healthcare worker. It is available from:

Healthline Aerosol Medicine
4610 Littlejohn Street
Baldwin Park, CA 91706
Tel: (877) 626-2626; Fax: (626) 960-8700

Features:

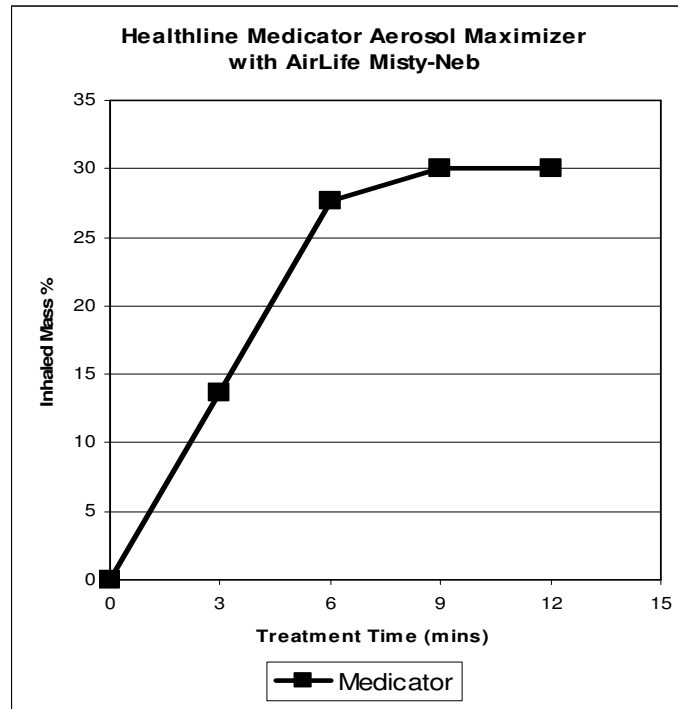
- Latex-free 1 L. reservoir bag (insures nebulized drug is inhaled rather than vented and wasted; promotes consistency of delivery to reduce variability of response and correct for differences in breathing pattern)
- Fine-particle nebulizer Allegiance AirLife Misty Max 10 (MMAD of ~1.25 μM insures appropriate particle size for peripheral deposition)
- Integral Exhalation Port Filter (protects caregivers against breathing exhaled aerosol)
- Noseclip (insures that patient inhales only through mouth to properly receive intended aerosol and prevent environmental contamination)



Use of the Medicator has been described in the peer-reviewed literature^{5,6,7}.

Aerosol Delivery with the high-efficiency Medicator Aerosol Maximizer:

With the use of the Medicator Aerosol Maximizer, a number of different dosing strategies are available. This is due to the fact that it is a high-efficiency device that delivers a greater total amount of drug, and has a higher delivery rate. The following plot of inhaled mass against time, for the Healthline Medicator Aerosol Maximizer with an AirLife Misty-Neb shows the increased total delivered drug and higher delivery rate⁸:



For reference, recall from the earlier discussion that the Respigard II typically delivers an inhaled mass of about 11% of the drug placed in the nebulizer, or about 33 mg of pentamidine. From the graph above, the performance of the Medicator with the AirLife Misty-Neb at different treatment times can be summarized thusly:

- Inhaled Mass in 3 minutes = 13.6% of prescribed dose (amount placed in nebulizer)
- Inhaled Mass in 6 minutes = 27.6% of prescribed dose (amount placed in nebulizer)
- Inhaled Mass in 9 minutes = 30.0% of prescribed dose (amount placed in nebulizer)

Therefore, delivered dose (inhaled mass of drug in mg) can be approximated for different treatment times and nebulizer loading doses:

Prescribed Dose (mg)	Treatment Time (mins)	Inhaled Mass (%)	Inhaled Mass (mg)
300	3	13.6	40.8
300	6	27.6	82.8
300	9	30.0	90.0
150	3	13.6	20.4
150	6	27.6	41.4
150	9	30.0	45.0
100	3	13.6	13.6
100	6	27.6	27.6
100	9	30.0	30.0

Dosing Strategies Based Upon Performance of Medicator Maximizer

The use of the Healthline Medicator Maximizer, with the AirLife Misty-Neb or Misty-Max 10 nebulizer, will provide a variety of dosing strategies so that patient needs can best be accommodated while assuring drug delivery that equals or exceeds that which is achievable with the Respigard II nebulizer. Time-saving strategies may be appropriate in children who will not tolerate lengthy treatment times or in debilitated patients who may fatigue quickly with conventional nebulizer therapy. Drug cost-saving strategies may be appropriate for home-care patients or others with inadequate insurance to cover the medication. A maximum drug delivery strategy may be appropriate in selected patients undergoing treatment for *Pneumocystis carinii* pneumonia.

Time-saving strategy:

From the chart above, it can be seen that a 3 minute treatment with a “prescribed dose” of 300 mg in the Medicator will achieve approximately 40.8 mg of pentamidine inhaled. This is about 124% the nominal dose delivered by a Respigard II nebulizer in 35-40 minutes (33 mg).

Drug cost-saving strategy:

From the chart above, it can be seen that a 6 minute treatment with a “prescribed dose” of 150 mg in the Medicator will achieve approximately 41.4 mg of pentamidine inhaled. This is about 125% the nominal dose delivered by a Respigard II nebulizer in 35-40 minutes (33 mg). Alternately, a 9 minute treatment with a “prescribed dose” of 100 mg in the Medicator will achieve approximately 30.0 mg of pentamidine inhaled. This is about 91% of the nominal dose delivered by a Respigard II nebulizer in 35-40 minutes (33 mg).

Maximum drug delivery strategy:

From the chart above, it can be seen that a 9 minute treatment with a “prescribed dose” of 300 mg in the Medicator will achieve approximately 90.0 mg of pentamidine inhaled. This is about 272% the nominal dose delivered by a Respigard II nebulizer in 35-40 minutes (33 mg).

Protocol

Policies:

1. Valid indications for nebulized pentamidine include patients with active documented HIV infection and/or AIDS, as well as patients who are receiving cancer chemotherapy.
2. A physician’s written order stating “Nebulized Pentamidine _____ mg at _____ frequency” is necessary to initiate this therapy. Ideally, the order should specify whether the treatment is for pneumonia therapy or prophylaxis. The order must comply with applicable hospital policies and regulations.
3. A respiratory therapist may draw up the prescribed dose of drug and place it in the designated nebulizer.
4. A respiratory therapist will administer the medication to the patient via the Healthline Medicator aerosol drug delivery system. Unused medication (nebulizer residual volume) must be properly disposed of through the process of rinsing the nebulizer after each treatment, according to departmental policy, but it is not necessary to log the amount or its disposal. However, the caregiver should wear gloves when rinsing the nebulizer to avoid skin contact with the unused pentamidine.

5. If the patient develops bronchospasm and wheezing during the nebulized pentamidine treatment, the treatment will be stopped and 2.5 mg of albuterol sulfate may be administered by SVN and the prescribing physician notified.
6. If it is established that the patient develops bronchospasm and wheezing during pentamidine nebulization, the respiratory therapist should contact the prescribing physician to have the order changed to allow 2.5 mg of albuterol sulfate to be administered by SVN prophylactically prior to the administration of nebulized pentamidine. DO NOT mix albuterol and pentamidine in the same nebulizer. It is better to pre-treat the patient with albuterol and confer protection against bronchial irritation in advance of inhaling the pentamidine. Also, the additional nebulizer volume of the albuterol will dilute the concentration of pentamidine in the nebulizer and prolong the nebulization time.
7. Treatments will be given at the prescribed frequency (usually once per day for treatment; once or twice a month for prophylaxis). Treatments will be given on the day shift only. Sleeping patients WILL BE awakened to receive their scheduled therapy. Orders for *prn* and stat treatments are not valid and will be ignored.
8. Attention must be paid to the total volume of solution in the nebulizer reservoir at the start of each treatment. Sterile water solution, quantity sufficient to make a total nebulizer volume of 3 mL, should be added as a diluent to the pentamidine powder to make the solution to be placed in the nebulizer. The total nebulizer volume should not exceed 3 mL so as to keep treatment time under 10 minutes in order to avoid patient fatigue.
9. The maximum allowable “dose” (nebulizer charge) under the protocol is 300 mg. The prescribing physician must be notified for confirmation if an order exceeding this amount is received.
10. Only the Healthline “Medicator Plus Aerosol Maximizer” aerosol drug delivery system, with exhalation filter, should be used for administering nebulized pentamidine in order to achieve an inhaled mass of at least 30 of the nebulizer charge with the appropriate particle size distribution.

Equipment and Supplies:

1. Healthline Medical #AM-602 Medicator Plus aerosol drug delivery system with mouthpiece and noseclip.
2. Optional Healthline closed aerosol mask if patient can not use a mouthpiece.
3. Optional Medicator Convenience Kit to extend mouthpiece or mask
4. Oxygen or Medical Air flowmeter as appropriate.

Procedure:

1. Verify the exact order in the patient's medical record.
2. Obtain proper dosage of drug and place in nebulizer reservoir. Prepare the drug (Nebupent or Pentam) by adding the appropriate amount of diluent as required. Mix well.
3. Introduce yourself and ask the patient what his or her name is and check the identification band on the patient's wrist for confirmation.
4. Conduct appropriate patient/family education and explain the specific details of the procedure you are about to have the patient do. Explain to the patient the need to keep the mouthpiece and

noseclip properly situated to avoid leakage of the drug. Instruct the patient to signal you to turn off the gas flow to the nebulizer before removing it from their mouth if he/she wishes to remove the mouthpiece for rest or cough. Instruct the patient to attempt to warn caregivers prior to a cough and how to cough into tissue to preclude the spread of exhaled droplets and particles.

5. Depending on the educational assessment of the patient, consider giving a “training treatment” with saline prior to actually giving the first pentamidine treatment. This will help assess the patient’s coordination and ability to follow the instructions above.

6. Check for asthmatic history and prepare to give bronchodilators prophylactically or if bronchospasm develops.

7. Assemble the Healthline Medicator Plus aerosol delivery system making sure that all connections are tight. Attach the nebulizer that has just been filled with the prescribed amount of pentamidine to the nebulizer port on the Medicator manifold and hook up the supply gas source.

6. Ascertain that the appropriate filter is connected to the exhalation port of the Medicator manifold.

7. When the patient is ready to begin inhaling the drug, adjust the air or O₂ flowmeter to 7 L/min and allow the patient to begin breathing from the system.

8. Place noseclip on the patient’s nose to encourage mouth breathing only. Coach the patient to breathe slowly and deeply, if possible. Instruct the patient to signal you if he/she wishes to temporarily stop the treatment in order to rest. Turn off the flowmeter just before the mouthpiece or mask is removed.

9. Observe the patient for signs and symptoms of adverse reactions to the medication and/or the procedure:

a. If the pulse rate changes by more than 25% during the treatment, stop the therapy, notify the nurse to help monitor the patient, notify the physician to report the adverse reaction, and include the details of the adverse reaction (including who was notified) in your written treatment note.

b. If bronchospasm or wheezing develops, stop the therapy, notify the nurse to help monitor the patient, notify the physician to report the adverse reaction, and include the details of the adverse reaction (including who was notified) in your written treatment note. If permitted by specific order, standing order, or as part of the hospital-approved pentamidine protocol, administer 2.5 mg of albuterol sulfate by small volume nebulizer.

10. At the conclusion of the treatment, it will not be possible to assess the patient for achievement of therapeutic outcomes. However, the patient should be assessed for their ability to cooperate, their psychomotor skills applicable to taking the treatment and for any adverse events occurring during the treatment:

a. If applicable, assess the patient for dyspnea or breathlessness according to hospital-accepted dyspnea scale.

b. If applicable, assess the patient for pain according to hospital-accepted pain assessment scale.

c. If applicable, assess the patient for the presence or absence of wheezing and

bronchospasm.

Include the results of all applicable patient assessments in your written treatment note.

11. At the conclusion of the treatment, any residual medication remaining in the nebulizer must be rinsed out of the nebulizer reservoir with sterile water. Shake as much of the residual water out of it as possible. Dry the nebulizer reservoir and jet with air or oxygen, reattach the nebulizer to the Medicator manifold, and store the entire assembly in a plastic bag labeled with the patient's name and room number. It is not necessary to rinse the Medicator manifold or reservoir bag.

12. Complete the necessary forms and records for recording patient therapy in the patient's medical record and/or hospital or departmental computerized information system.

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