Occupational Risk Prevention in Aerosol Therapy (pentamidine, ribavirin)

Consensus paper
from the basic German and French documentation

Working document for occupational safety and health specialists

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In 1993, the Bureau of the ISSA Health Services Section created a Working group to study health risks related to the use of chemical products in the health sector. This Working group seats representatives from the German Institution for statutory accident insurance and prevention in the health and welfare services (BGW, R. Ahrens and U. Eickmann), the French National research and safety institute (INRS, M. Falcy), the French Regional health insurance fund (CRAM de Bretagne, L. Beaudouin), and the Swiss National accident insurance fund (Suva, M. Rüegger and M. Jost, the Working group's chairman).

This paper has been developed as a consensus statement from the basic German[1] and French[2] documentation on the prevention of occupational risks in pentamidine and ribavirin aerosol therapy generated by the Chemical products Working group of the ISSA Health Services Section in 1997. It summarizes the Working group's thinking on occupational risks and applicable preventive measures in aerosol therapy.

The consensus document deals mainly with problems stemming from the administration of aerosols produced by nebulizers generating particles that are generally 1 to 3 mm in diameter. The most important applications insofar as occupational risk prevention is concerned are prophylaxis of Pneumocystis carinii *pneumonia by pentamidine, and the use of ribavirin in pediatrics. Other drugs are administered by the same process, such as those used in treating diseases of the upper and lower respiratory tract as well as antibiotics, and this form of administration is probably going to develop for new types of drugs. The risk assessment approach and recommended preventive measures presented here can be transposed to other applications with the necessary adaptations. The use of mist or powder aerosols in the treatment of bronchial asthma and obstructive pulmonary diseases will not be discussed here as these treatments, which the patients self-administer under instructions from the health care workers, are of no risk to these workers if practiced correctly.*

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Contents

1. Specific problems of aerosol therapy workplaces

Aerosol therapy is commonly used for administering certain drugs, and its use is not limited to health care establishments or doctors' offices. It is also applied in home care, and for individual use. The drugs employed are often very active, and the therapy involves a drug-patient-environment system that generally cannot be totally closed, so the health care personnel, other patients, and the work environment are more or less subject to exposure. While aerosol therapy is mainly applied for local treatment of respiratory tract diseases, it is also used today for administering drugs with systemic effects.

1.1. General data

Aerosols are systems comprising several phases, consisting of a gas (mainly air) and solid or liquid particles dispersed in this gas. The mass median aerodynamic diameter (MMAD) of airborne aerosol particles is generally between 0.001 and 100 µm. The smaller this diameter, the greater the risk of the particles becoming airborne and the longer they take to deposit. An aerosol consisting of particles of less than 1µm behaves practically like a gas, with the particles depositing only if there is no air movement. Up to a diameter of 10 µm, particles can become airborne.

The MMAD is a fictitious value defined by reference to a particle model whose specific weight is equal to that of water. The MMAD of an aerosol particle of any shape and density is the diameter of a sphere whose density is equal to unity (i.e. 1 g/cm3) that would have the same re-deposition velocity as the particle, whether in the absence of turbulence or in a laminar flow.

It is the particle diameter that determines deposition at the targeted pulmonary site. Particles of more than 10 µm deposit in the upper part of the respiratory tract. In order for the therapeutic action to occur at the level of the lower respiratory tract, a diameter of 2 to 5 µm is optimum. The diameter must be between 0.8 and 3 µm in order for the product to act on the pulmonary parenchyma. Aerosol particles whose diameter is less than 0.5 µm reach the alveoli but are then re-exhaled.

For sampling purposes, and also for establishing exposure limits, many countries distinguish between the respirable fraction of the aerosol and its alveolar fraction.

1.2. Therapy using aerosols

Aerosols of 1 to 3 µm are used for alveolar aerosol therapy. These are produced by a jet or ultrasonic nebulizer, or are delivered by dry powder or metered dose inhalers so that the physical properties of aerosols can largely be standardized. As the human nose is a very efficient filter for aerosols, these should be inhaled by the mouth as far as possible.

As a general rule, aerosol therapy systems are more or less open, so that a part of the administered drug is breathed back out into the ambient air in the absence of 100 % effective filtration or extraction devices. Products are also released into ambient air when the nebulizer system is separated from the patient. These disconnections are favored by the cough-producing action of certain aerosols.

1.3. Risk assessment

Experience shows that drugs are often used without there being sufficient data concerning the risks involved for the workers who administer them. Especially in the case of aerosol therapy, employees are exposed directly to the products by inhalation.

The occupational risks must therefore always be assessed in co-operation with the specialists concerned: mainly, safety officers, occupational physicians, hygienists, in-house physicians, or persons in charge of health care worker supervision. National regulations must of course be observed.

The first stage in risk assessment consists in using the toxicological data available concerning the drug, including its carcinogenic, mutagenic and teratogenic properties. For this purpose, the following sources are available:

- Results of clinical studies on the use of these aerosols, published in the specialized literature; case studies of side effects and the effects on the health of patients and workers
- Data banks on the toxicology and pharmacology of drugs
- Pharmacological and toxicological data available from the drug's manufacturer

Aside from characterizing the drugs from the viewpoint of their biologically active components, clinical analyses of the effect of therapeutic doses (whether it be of the action sought or of the side effects observed) are of great interest. Case studies from occupational physicians mentioning damage to personnel health are also a major source of information.

Data concerning the design and layout of aerosol therapy rooms also need to be analyzed for risk assessment purposes, as do the organizational procedures followed. The data from air and biological monitoring performed in similar work areas should be looked up. As there generally are no occupational exposure limit (OEL) values for pharmaceuticals that can be compared with measured air concentrations or biological parameters, exposure is assessed from data concerning the dose-effect relationship in therapeutic use.

New risk assessments must imperatively be made mainly in the following cases:

- Installation of a new aerosol therapy unit
- Implementation of new aerosol generation or administration methods
- Use of new aerosolized drugs
- Disorders reported by health care workers after exposure to the drugs
- Presumption of a risk due to modification of the room or its ventilation system

Alveolar deposition of the drugs is always accompanied by bronchial deposition of cough producing larger-sized particles. When the patient exhibits an infectious disease, the personnel may then be exposed to airborne infectious agents in the droplets expectorated in coughing.

The risk assessment may lead to the establishment of a checklist for systematic evaluation of safety and health protection at the workplace.

2. Risks for health care workers in pentamidine and ribavirin aerosol therapy

Aerosolized **pentamidine** (Pentacarinat®) is used for the prevention and treatment of *Pneumocystis carinii* pneumonia (PCP), especially in cases of acquired immunodeficiency, *e.g.* AIDS patients. It is recommended today for patients who cannot withstand the side effects of the trimethoprim-sulfamethoxazole association, which is the choice treatment for this disease.

Ribavirin (Virazole®) is mainly used in the treatment of respiratory syncytial virus (RSV) infections in children and in organ recipients to whom an immunosuppressive treatment is administered.

2.1. Pentamidine and ribavirin: major properties for occupational risk prevention

2.1.1. Pentamidine

Animal experiments have brought out no carcinogenic effect. No definite data is available concerning any mutagenic, carcinogenic or teratogenic effect of pentamidine on humans. *In vitro* mutagenicity tests on mammalian somatic cells indicate low activity after metabolic activation. However, there is currently no study available showing a genotoxic risk for humans.

As other folate antagonists like aminopterin and methotrexate cause an increase in spontaneous abortions and malformations, similar effects from treatment by pentamidine are to be feared by analogy. Experimentation shows that pentamidine can cross the placental barrier. An embryotoxic action has been observed in the rat.

No adverse effects in the course of human pregnancy have been described as yet. However, as reproductive effects are still inadequately studied, pentamidine prophylaxis is not prescribed for pregnant women.

In patients under pentamidine aerosol therapy, the following side effects have been observed: bronchospasm, cough, burning pain in the pharyngeal region, vertigo, fatigue, allergic reactions, notably at the level of the respiratory tract, skin and mucous irritation, metallic and bitter taste. Cases of pancreatitis, nephrotoxic effects, and hypoglycemia have also been described.

The immediate pathological manifestations in health care workers exposed to pentamidine aerosols do not seem to be severe. They correspond to the side effects described in the patients, except that no cases of pancreatitis, nephrotoxic effects, or hypoglycemia have been described. The disorders are reversible and can generally be avoided when the necessary measures are taken to improve working conditions.

No delayed effect in health care workers has been described to date.

2.1.2 Ribavirin

Animal tests and *in vitro* experiments have revealed a mutagenic, carcinogenic, teratogenic and embryolethal potential in ribavirin.

To date, no carcinogenic or mutagenic action on humans has been reported, nor any adverse pregnancy outcome among persons exposed.

No serious side effects have been described in children under ribavirin aerosol therapy. The following symptoms have been observed in adults, however: irritation of the conjunctivae and nasal and pharyngeal mucous membranes, dryness of the mucous membranes in the upper airways, cough, respiratory distress, impairment of pulmonary function in patients with chronic obstructive pulmonary disease or bronchial asthma, chest pain, cardiovascular problems with drop in blood pressure and collapse, and skin rashes.

Certain health care workers present in the aerosol therapy room complain of irritations of the eyes and upper and lower airways, as well as headaches, when exposed to ribavirin. The effects are felt to be of minor importance and quickly subside after the exposure.

2.2. Infectious risk

The administration of aerosolized pentamidine or ribavirin in prophylaxis or treatment of pulmonary diseases includes a risk of airborne transmission of infectious disease to the health care worker.

The problem arises especially in the case of pentamidine prophylaxis in AIDS patients. This group of patients exhibits a high prevalence of tuberculosis, which gives rise to particular concern when due to multidrug-resistant strains of *Mycobacterium tuberculosis*. In workers in contact with patients under pentamidine aerosol therapy, the frequency of tuberculous infections is higher than in hospital personnel as a whole.

2.3. Assessment of health care worker exposure

Available studies on pentamidine and ribavirin air concentrations around aerosol therapy units, and biological monitoring data give an idea of worker exposure.

Exposure can be seen as two types:

- Relatively high exposure during therapy, with high concentrations for very short time periods, the duration of which depends on the operating procedure, inhalation techniques, and patient behavior.
- Relatively low background exposure, observed even when the drugs are administered correctly and the engineering and administrative controls and personal protection measures are applied.

The available metrological data confirm that the internal loads of pentamidine and ribavirin in health care workers, which are generally very low compared with the therapeutic doses, depend mainly on exposure peaks.

There is no OEL value for *airborne pentamidine concentration* at the workplace. The concentrations measured are generally less than 70 $\mu g/m^3$, with major differences depending on the case. The values measured over an eight-hour shift have shown that health care workers' exposure is low compared with the therapeutic doses. High concentrations can be expected– as much as 400 times the background level has been measured – when disconnections occur during the administration.

Biological monitoring reveals the presence of *urinary* pentamidine, especially when the health care worker is exposed repeatedly to concentration peaks over short periods.

For the *airborne ribavirin concentration*, a provisional limit of 2.7 $\mu g/m^3$ exists in the United States (California Department of Health Services, Occupational Health Program; Environmental Protection Agency). In the absence of data on reproductive toxicity in humans, this indicative value is based on the results of embryolethality testing in particularly susceptible laboratory animals. When this time-weighted average (TWA) indicative value is complied with, there should be no reproductive effects in humans. Values of 50,000 to 90,000 $\mu g/m^3$ have been measured under inhalation tents or hoods. Values measured by individual sampling outside the inhalation tents or hoods ranged from "non-detectable" to about 1000 $\mu g/m^3$, depending on the mode of administration. When the engineering controls and personal protective measures recommended in section 3 are correctly applied, concentrations of the order of 2 to 60 $\mu g/m^3$ are generally measured. It should nonetheless be noted that workers do not come within the immediate proximity of the aerosol administration site except for short periods during a normal workday, so their exposure is low compared with the therapeutic doses. Few studies have been published on this question, though.

For *biological monitoring* purposes, ribavirin levels can be measured in *urine*, *plasma*, and red *blood cells*. To date, no biological exposure limit values have been published to which measured concentrations can be compared. It should be noted that the few data published vary considerably according to the mode of drug administration. According to data from the literature, the urinary ribavirin level is below the detection limit in most workers when working conditions are satisfactory.

2.4. Assessment of risks to health care workers

The presence of *pentamidine* in ambient air may be due to the exhalation of the drug by the patients, to leaks, or to disconnections in the course of treatment. Air and biological monitoring have shown that exposure and internal dose are generally very low in health care workers, compared with therapeutic doses. The internal dose depends essentially on exposure peaks resulting from disconnections. The manifestations described to date in health care workers are generally reversible and occur when the work environment is especially unfavorable. These manifestations are mainly irritation of the conjunctivae and upper and lower airways, and respiratory and skin allergies. No long-term effect has been reported to date in health care workers. The most important aspect is an increased risk of tuberculosis in workers in charge of administering pentamidine.

So it is essential to reduce the risk of tuberculosis transmission, prevent irritations of eyes and airways, and avoid exposure of pregnant women, in the absence of sufficient data on any risks there may be during pregnancy.

When administering *ribavirin*, worker exposure depends mainly on the technical measures used at the level of the aerosol administration systems. When a double containment exists with a scavenging system in the volume separating the two containment barriers, the worker is exposed only when action is taken on the patient during treatment. The exposure and internal dose are low compared with therapeutic doses when appropriate technical measures are employed. Until now, only reversible effects have been observed in workers, and these concerned mainly the conjunctivae and airways. No long-term effect has been described. According to available toxicological data, there may exist a risk during pregnancy, although no case of adverse outcome related to occupational exposure to ribavirin has been described. Prevention should emphasize the use of appropriate aerosol administration systems allowing reduction of exposure.

3. Recommended engineering and administrative controls, and personal protective measures

The measures proposed should make it possible to keep health care worker exposure to drugs and to agents responsible for airborne infectious diseases as low as possible during patient treatment and care.

The usual hierarchy of preventive measures will be applied at aerosol therapy administration units: engineering controls (*e.g.* those concerning the premises, ventilation, or the aerosol generator) have priority over administrative controls, which in turn have priority over personal protective measures.

In designing aerosol therapy units in hospitals and other health care establishments, the employer and those responsible for occupational safety and health must set the objective of minimizing exposure through optimization of engineering controls.

Recommendations published in the specialized literature on occupational risk prevention at aerosol therapy workplaces are based especially on the Aerosol Consensus Statement of the American Association for Respiratory Care, the guidelines of the British Occupational Hygiene Society, and those of the Centers for Disease Control (US Department of Health and Human Services) for the prevention of tuberculosis.

3.1. Pentamidine

3.1.1. Engineering controls

The technical measures aim to keep health care worker exposure as low as possible, mainly when it is necessary to enter the treatment chamber after disconnections, and to prevent tuberculous infection. It should be remembered that the treatment time is short (about 30 minutes), and that there is a high patient turnover, which means that the air should be changed quickly.

The following recommendations should be retained:

- Treatment should be applied in individual rooms or cabins.
- For ventilation purposes, the recommended number of air changes differs according to the source (six per hour for the Centers for Disease Control, and 20 for the British Occupational Hygiene Society). Considering the objectives to be achieved, it seems desirable to adopt the higher value for the ventilation system design. The blowing and exhaust devices should be arranged to optimize air change.
- Air should be exhausted to the outside or filtered through a high-efficiency particulate air (HEPA) filter.
- A negative pressure should be maintained in the room.
- Patients and staff should be able to communicate actively, for example through a calling system.

- All surfaces in the room should be easy to clean and disinfect.
- The aerosol generator used should have an exhalation filter and a cut-off switch actuated by the patient, and/or automatic shutdown when the mouthpiece is removed from the patient's mouth.
- The aerosol particles should be of optimum size (less than 3µm) for better alveolar deposition and reduction of the cough-producing effect.

3.1.2. Administrative controls

- Instructions should be issued indicating the possible risks as well as the preventive measures and applicable rules of behavior.
- These instructions will serve as a basis for staff training before taking the job, or if procedures are modified, or during regular training periods.
- The staff should not remain in the room during aerosol therapy aside from brief interventions for assistance or control purposes that maybe necessary.
- A visual device outside the room should indicate that treatment is in progress.
- The nebulizer should be properly maintained.
- In the absence of any precise data concerning reproductive risks, exposure of pregnant women or those planning pregnancy should be avoided.
- The necessary time should be taken to give patients precise instructions, mainly concerning the use of the nebulizer, the need to limit the number of disconnections, and the behavior to be adopted in the case of a coughing fit. In particular, it should be recommended to patients that they shut off the nebulizer before calling the health care staff at the time of a coughing fit or disconnection.
- The staff should be especially attentive to the cases of patients who need to remove their mouthpiece frequently during treatment. Windowed doors should be installed to allow appropriate visual surveillance.
- Cleaning personnel should be informed of the need to use wet cleaning for rooms where aerosols are administered, to avoid raising dust.
- When aerosolized pentamidine is administered to patients suffering from infectious tuberculosis, the treatment should be applied in the patient's isolation chamber.
- The ventilation system should remain in operation after the end of treatment. Health care workers should not enter the room without respiratory protection for 30 minutes thereafter.

3.1.3. Personal protection

Health care workers administering pentamidine aerosols should wear FFP2 respirators. Common surgical masks do not provide enough protection. The staff should wear this equipment when major exposure is foreseeable for care purposes, in case of violent coughing fits, in cases of patients having difficulty to co-operate, or for any action to be taken on the nebulizer.

For other personal protective equipment, the choice is made on a case-by-case basis according to the infectious risk involved.

3.2. Ribavirin

3.2.1. Engineering controls

The following measures are recommended:

- Treatments should be administered in individual rooms or cabins.
- In the same way as for pentamidine (see section 3.1.1), effective ventilation should be provided. Considering the objectives to be achieved, it seems desirable to adopt a ventilation system design allowing 20 air changes per hour as recommended by the British Occupational Hygiene Society.
- The blowing and exhaust devices should be arranged to optimize air exchanges.
- Air should be exhausted to the outside or filtered through a HEPA filter.
- A negative pressure should be maintained in the room.
- A double containment should be used for aerosol therapy in the case of non-ventilated patients. The air extracted from the scavenging region separating the two containments should be discharged outdoors or through a HEPA filter. In the case of ventilated patients, the exhaled air should be filtered.
- It should be possible to shut off the nebulizer from outside the treatment room before any action is taken with the patient.
- All surfaces in the room should be easy to clean and disinfect.

3.2.2. Administrative controls

The measures recommended here are on the whole the same as for pentamidine aerosol therapy (see section 3.1.2). The following points nonetheless require emphasis:

- Instructions should be issued indicating the possible risks as well as the preventive measures and applicable rules of behavior.
- These instructions will serve as a basis for staff training before taking the job, or if procedures are modified, or during regular training periods.
- Pregnant women, those planning a pregnancy, and breastfeeding women should not be exposed.
- When it is necessary to enter the aerosol therapy chamber in a case of emergency, before or immediately after the nebulizer is shut off, it can be assumed that significant concentrations of ribavirin subsist, and it is thus essential that a FFP2 respirator and protective goggles be worn.

3.2.3. Personal protection

Aside from the cases mentioned above, and when the above engineering and administrative controls are effectively complied with, the wearing of personal protective equipment is not necessary for the health care workers who have to enter the aerosol therapy room.

3.3. First-aid measures in the case of eye or mucocutaneous contact with pentamidine or ribavirin

After eye or mucocutaneous contact with pentamidine or ribavirin, immediately wash the contaminated parts in abundant running water.

Change highly contaminated clothing.

In case of contact with eyes, rinse for at least ten minutes in abundant running water and seek medical advice.

Report the accident.

In case of local symptomatology consecutive to mucocutaneous contact, seek medical advice.

4. Recommendations for the medical surveillance of health care workers

The personnel exposed to pentamidine or ribavirin aerosols must undergo medical surveillance. This can be conducted in the framework of systematic health care worker medical surveillance. The purpose of this medical surveillance (with clinical examination and possible complementary tests) is to report health damage related to pentamidine or ribavirin aerosols, to assess working conditions and risks of exposure, and to improve worker awareness of drugs and how to handle them. National regulations applicable to preventive medical examinations are to be complied with.

Generally, a medical examination should be performed before hiring or assignment to this type of work. The interval between two examinations depends on the regulations in force as well as the specific features of the workplace. The examination should include a medical and occupational history and a clinical examination, especially of the conjunctivae and upper and lower airways; additional examinations, such as pulmonary function tests, may also be deemed necessary. Special attention should be paid to people having a history of bronchial asthma or bronchial hyperreactivity.

The preventive medical examination may be complemented by biological monitoring.

The risk of airborne infectious diseases is a major aspect of medical surveillance. The health care workers in charge of pentamidine aerosol therapy have a significantly higher risk of tuberculosis, so it is advised to apply a tuberculin test at hiring, and then at least once per year. If a seroconversion is observed after contacts with patients suffering from infectious tuberculosis, a preventive treatment should begin. At the current time, six months' treatment on isoniazide is recommended. In workers having a diagnosis of tuberculosis requiring treatment, this should be practiced according to regulations in force in the country concerned.

When health care workers have been in contact with patients in aerosol therapy who are subsequently diagnosed with infectious tuberculosis, the work colleagues and family of the workers exposed must undergo surveillance.

It is incumbent upon the occupational physician to consider and request the necessary restrictions to employment. Especially in the case of pregnancy, a talk with the occupational physician should make it possible to decide between maintenance on the job or termination as soon as pregnancy is known and, preferably, even as soon as it is planned.

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