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Inhalation of tobramycin in cystic fibrosis Part 1: The choice of a nebulizer

P.P.H. Le Brun [a,*], A.H. de Boer [b], D. Gjaltema [b], P. Hagedoorn [b], H.G.M. Heijerman [c], H.W. Frijlink [b]

[a] *Central Hospital Pharmacy The Hague, P.O. Box 43100, 2504 AC The Hague, The Netherlands*
[b] *Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands*
[c] *Adult Cystic Fibrosis Center, Department of Pulmonology, Leyenburg Hospital, The Hague, The Netherlands*

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Abstract

Forteen commercially available jet and ultrasonic nebulizers were investigated with the aim to select the most suitable type of apparatus for the inhalation of a 10% tobramycin solution. Two different techniques for measurement of particle size distribution were evaluated: laser diffraction and cascade impactor analysis. The final selection of the nebulizers is based on particle size distribution, output and stable performance during nebulization. All 14 nebulizers (eight jet and six ultrasonic) were filled with a solution of 10% m/v tobramycin (as sulphate) in water. The volume in the tested devices ranged from 4.5 to 10 ml (= 450–1000 mg tobramycin) in accordance with the prescribed usage by the suppliers. The nebulizers were connected with a special designed adapter to a laser diffraction analyser in order to measure particle size distribution of the aerosol. Inhalation was simulated with a static flow of 40 l/min. The particle size distribution (expressed as X_{10}, X_{50}, and X_{90}) was determined after 10 s, 1.5, 3, 4.5, 6, 9 and 12 min of nebulization. Furthermore, the tobramycin solutions were assayed for tobramycin content before and after nebulization. For all nebulizers, the mean particle size distribution, depicted as X_{50}, was within the range of 1–5 mm. There were no relevant differences between the nebulizers in concentration or particle size distribution during nebulization. The output of the nebulizers is a result of both nebulization and evaporation. The output, expressed as volume of tobramycin solution, ranged from 0.06 to 0.50 ml/min. The output of tobramycin ranged from 1.2 to 39.5 mg/min. For clinical practice 300–600 mg have to be nebulized within 20–30 min. It was concluded that only three jet nebulizers [Porta-Neb Sidestream (PNS), Porta-Neb Ventstream (PNV) and Pariboy Pari LC+ (PLC)] have a reasonable output and an acceptable particle size distribution for the administration of a 10% tobramycin solution in the therapeutic dosage range.

Keywords: Jet nebulizer; Ultrasonic nebulizer; Tobramycin; Drug output; Particle size distribution; Laser diffraction analysis; Cystic fibrosis

Abbreviations: CIR, Cirrus; DVH, DeVilbiss Pulmo-Aide T updraft; DVS, DeVilbiss Pulmo-Aide Sidestream; FLS, Freeway Lite Sidestream; MCR, MicroCirrus; MSJ, Medasonic Systam Junior; MSO, Medix Sonix 2000; MSR, Medasonic Senior; MSS, Medasonic Systam Senior; OMU, Omron Ultrasonic; PLC, Pariboy Pari LC+; PNS, Porta-Neb Sidestream; PNV, Porta-Neb Ventstream.

* Corresponding author. Tel.: +31-70-321-7217; fax: +31-70-321-7110.

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1. Introduction

Inhalation of antibiotics is a regular part of current cystic fibrosis (CF) therapy. It has been demonstrated that in clinically stable CF-patients with chronic Pseudomonas infection, inhalation of antibiotics improves or slows down the detoriation of lung function and decreases the number of exacerbations. Many centers have adopted inhalation of antibiotics as a standard therapy.

In the studies on inhalation a variety of antibiotics and a wide range of dosages were investigated and different nebulizers were used in different patient populations, leading to an inconsistency in the results (Touw et al., 1995; Mukhopadhyay et al., 1996).

Recently the safety and efficacy of a tobramycin solution for inhalation was demonstrated in a placebo controlled trial in the maintenance treatment of CF patients (Ramsey et al., 1999). Improved pulmonary function, decreased bacterial burden and reduced risk for hospitilization were found in patients receiving 300 mg of inhaled tobramycin twice daily during three courses of 28 days. Serum tobramycin levels were approximately 1.0 mg/l, measured 1 h after inhalation of 300 mg tobramycin with a Pari LC+ jet nebulizer. Serum levels were measured on day 3 and 10. In another pharmacokinetic study, plasma levels varied from 0.19 to 2.57 mg/l after a single inhalation of 600 mg tobramycin with an ultrasonic nebulizer (Touw et al., 1997). From these and other reports, (Huet and Nivelon, 1997; Webb and Dodd, 1997) it is concluded that further investigations are needed to establish the optimal tobramycin dose for nebulization of a solution.

It is known that there is a difference in the performance of nebulizers, reflected in varying drug output rates, droplet size distributions and in the deposition of active drug substance in the lungs. The output rate of nebulizers can be described by the aerosolized volume or the aerosolized mass of drug (Newman, 1989). The nebulized volume can be determined simply by weighing the nebulizer before and after use. Results may be misleading because they do not take into account the increase in drug concentration within the nebulizer by evaporation of the solvent. Therefore drug output rate in mg/ml is a better parameter for the nebulizer output.

Furthermore, the performance of a nebulizer is determined by the droplet size distribution of the aerosol cloud. In general, droplets with a diameter of 1–5 mm are assumed to be the respirable fraction of an aerosol (Mattews and Doershuk, 1967; Newman and Clarke, 1983). This fraction may be deposited in the large and small airways and the alveoli by impaction and sedimentation. Droplets larger than 5 mm will impact in the upper airways, whereas particles smaller than 1 mm are known to be partly exhaled again.

Other relevant characteristics of the nebulized solution are the osmolality and pH. Their value should be within a physiological range in order to prevent airway irritation.

Therefore, effective aerosol therapy is to a significant part dependent on the nebulizer used. It is also reported that for each nebulized drug or drug combination the most efficient nebulization system has to be established (Hurley et al., 1994; Newman et al., 1994; Faurisson et al., 1996; McCallion et al., 1996; Coates et al., 1997; Devadason et al., 1997; Weber et al., 1997).

For the clinical treatment of CF patients, a reliable nebulizer is needed to aerosolize tobramycine. It was intended to treat patients with an iso-osmotic tobramycin solution without additives. Since a 10% solution is almost iso-osmotic, this concentration was chosen in the experiments. Using the 10% tobramycin solution, the characteristics of 14 commercially available jet and ultrasonic nebulizers were compared.

The aim of this prelimenary study was to select the most suitable nebulizer for a 10% tobramycin solution. The following performance requirements were used for the selection:

- a mean droplet size in the range from 1 to 5 mm with the smallest possible deviation
- a high output of drug substance
- a stable performance during the entire nebulization time

2. Materials and methods

2.1. Drug solution

In other studies, 4–6% tobramycin solutions with additives for osmolality and, sometimes, with preservatives were used. In this study, a 10% tobramycin (as sulphate) solution without additives was investigated. It can be calculated that a 10% solution is almost iso-osmotic. Tobramycin sulphate (USP XXIII, Pharmacin International, Zwijndrecht, The Netherlands) was dissolved in water for injection.

The pH (Radiometer, Copenhagen, Denmark) and osmolality (Osmometer Knauer 4050, Wilton, Etten Leur, The Netherlands) were determined.

2.2. Devices

2.2.1. Jet nebulizers

Jet nebulizers consist of a nebulizing chamber in which an aerosol is generated with a flow of gas provided by a compressor or a pressurized air system.

The following compressor and jet nebulizer combinations were compared: Porta-Neb Sidestream® (PNS), Porta-Neb Ventstream® (PNV), Freeway lite Sidestream® (FLS) (all by Medic-Aid, Romedic, Meersen, The Netherlands), DeVilbiss Pulmo-Aide Sidestream® (DVS), DeVilbiss Pulmo-Aide Hudson T Updraft® (DVH) (both by Tefa, Nieuwegein, The Netherlands), Cirrus® (CIR), MicroCirrus® (MCR) (Maxxim Medical, Den Bosch, The Netherlands) and Pari Boy Pari LC plus® (PLC) (Huisman, Tiel, The Netherlands).

The CIR and the MCR are conventional nebulizers intended for single use in hospitals. These nebulizers are driven by a source of compressed air and controlled by a flow meter. The other nebulizers are used at home in combination with a mechanical compressor. The Hudson T Updraft is a coventional jet nebulizer. The Sidestream is a device with an extra open vent which results in a continuously greater air flow through the chamber. The larger air flow results in an increased number of small particles to be generated within a given time. This leads also to a greater loss of aerosol during exhalation which is a disadvantage as compared to the conventional type.

The Ventstream and the Pari LC plus are 'breath assisted, open vent' nebulizers. During inhalation an extra vent opens and, as with the Sidestream, extra air will be drawn through the nebulizer. During exhalation the inspiratory valve closes and only the flow of the compressor remains. Loss of aerosol is therefore minimized during exhalation. Furthermore, exhaled air passes out through a seperate expiratory pathway (O'Callaghan and Barry, 1997).

2.3. Ultrasonic nebulizers

Ultrasonic nebulizers are devices driven by electrical power in which an aerosol is generated by high frequency vibration, causing the liquid surface to disrupt into a fine mist.

The following ultrasonic nebulizers were compared: Wisto Senior® (Wisto, Woerden, The Netherlands), Medasonic Senior Venti-cup® (MSR), Medasonic Systam Senior® (MSS), Medasonic Systam Junior® (MSJ) (all by Medasto, Woerden, The Netherlands), Medix Sonix 2000® (MSO), Omron NE-U07® (OMU) (both by Huisman, Tiel, The Netherlands)

2.4. Particle size analysis of the aerosol cloud

Two different techniques were used for measurement of the particle size distribution of the droplets in the aerosol cloud from the PNV: laser diffraction and cascade impactor analysis. All other nebulizers were characterized with laser diffraction analysis only. Laser diffraction data for the PNV, FLS and DVS combination were calculated with both the Fraunhofer and Mie theory. Diffraction data obtained with the other devices were calculated with the Fraunhofer theory only (for reasons explained in Section 3).

For the laser diffraction analysis, a Sympatec HELOS Compact, model KA with a 100 mm lens for the size range 0.9–175 mm was used (Sympa-

tec GmbH, Clausthal-Zellerfeld, Germany). In order to standardize laser diffraction analysis, a special adapter was developed to which the nebulizer mouthpiece was attached. The adapter could be tilted and had an exchangeable front in order to accept all 14 nebulizers used in the study, having all different lengths, angles and shapes of their mouthpieces. The adapter was fixed to the support in the measuring zone between the laser diffraction cabinets, thus to keep the distance between the nebulizer's mouthpiece and the laser beam constant at 6.5 cm. Behind the adapter was a liquid impinger for the separation of droplets from the air stream. The closed combination was connected to a vacuum system, including a flow controller and Venturi-meter, for accurate adjustment of an inspiratory flow rate of 40 l/min through the nebulizer.

The nebulizer cups were filled either with the volumes prescribed by the supplier of the devices, or the mean of a recommended filling range. Volumes varied between 4.5 and 10 ml. Nebulization was continued up to (and including) a total inhalation time of 12 min, or shorter if the device began to sputter earlier. Droplet size distribution was not measured continuously, but 10 s, 1.5; 3; 4.5; 6; 9 and 12 min, respectively, after the start of nebulization. Measuring time at each time interval was 10 s. All nebulizers could be measured in triplicate according to these procedures, except for the Wisto and Medasonic senior which appeared to deposit droplets onto the lenses of the Sympatec during nebulization. Therefore, these two devices were disconnected from the adapter between a reduced number of time intervals, being only during 10 s; 6 and 12 min after the start of the nebulization, respectively.

The results from laser diffraction analysis have been expressed as X_{10}, X_{50} and X_{90}-values, being the diameters corresponding with respectively 10, 50 and 90% of total volume from cumulative percentage undersize curves.

For the cascade impactor analysis, a four stage glass constructed Lenz Labor impactor was used. The theoretical cut-off diameters of this impactor at 40 l/min for spherical aqueous droplets with unit density are 13.11 mm for the second and 6.47 mm for the third stage. The impactor was operated at the same flow rate of 40 l/min. Behind the fourth impinger stage, a filter was used in order to collect very fine droplets passing this final impactor stage. The PNV was connected to a special adapter on a dry bent inlet tube, constructed of glass. Continuous nebulization was stopped after a period of 4.5 min, or less if the device began to sputter within this time. For comparison with laser diffraction results, the fractions retained from all impactor stages and the filter were summarized and individual fractions were expressed in percentage of this sum. It was assumed (on the basis of experiences with dry powder inhalers) that particles deposited in the inlet tube have the same size distribution as the particles entering the impactor. Six analyses were performed with different filter systems behind the fourth stage.

2.5. Nebulizer output

The nebulizer output, described by the volume or amount of tobramycin nebulized was determined by measuring weight and concentration.

After nebulization the nebulizer was weighed and the nebulized volume was calculated using the density of the residual drug solution. Using the initial and the end concentration, the drug output rate in milligrams could be calculated. The nebulized output rate was expressed in ml/min and in mg/min.

Nebulization time was stopped after 12 min or earlier if the nebulizer began to sputter because of depletion of the solution. The 12 min period in the experiments is equivalent to less than 30 min of inhalation in practice considering inhalation and exhalation. Such a period is in general acceptable for most patients.

2.6. Tobramycin assay

The tobramyin concentration was determined using fluorescence polarization immunoassay (AxSYM, Abbot). The error of this method is less than 5%. Every sample was diluted 25 000 times to a concentration of approximately 4 mg/ml and measured twice. The concentration in the samples was calculated from the results of a standard solution of 10% tobramycin measured in the same run.

3. Results and discussion

It is difficult to compare particle sizing results from different studies. The set up of the equipment, the measuring equipment and its software, the characteristics of the drug solution and, in case of jet nebulizers, the used compressor all infuence the results. A standardized set up was designed to compare all devices under the same circumstances.

3.1. Particle size distribution

For comparison of the cascade impactor and laser diffraction results (from both Mie and Fraunhofer calculation) on the aerosol cloud from the PNV, an aquous 0.3% (m/v) solution of dinatriumcromoglycate (DNCG) was aerosolized as a test substance. This solution yielded somewhat coarser droplets from this nebulizer than a 10% tobramycin solution. The volume median diameter (equals mass median diameter: MMD) from laser diffraction measurements was 3.38 mm when calculated with Fraunhofer and 3.48 when calculated with Mie, using a real refractive index of 1.33 (for water) and an imaginary index of 0. For both theories, the X_{100}-value was 12.5 μm.

On the basis of the theoretical cut-off diameters of the impactor, all droplets were expected to deposit on the third and fourth impactor stage plus the filter. In practice, 95.6% of all particles entering the cascade impactor was retained from the third, the fourth stage and the filter, of which 13.9% was deposited on the third stage; 70.0% on the fourth stage and 11.7% in the filter (mean of all six duplicate experiments). From these results it was conclude that the impactor is not sufficiently discriminating between nebulizers, delivering droplets with a narrow size distribution and rather low MMDs compared to the cut-off diameters of the lower stages. Using this impactor for the study, it would be impossible to observe small differences between the nebulizers, since the majority of the droplets are deposited on only two stages (two size fractions).

The choice between Mie and Fraunhofer is not only a choice between two different light diffraction theories, but also a choice between the algorithms used for solution of the complex diffraction integrals. For small, (semi) transparant particles, Mie may be the better theory, but the deconvolution methods (including the smoothing techniques for suppression of oscillations) can introduce inaccuracies and decrease the resolution and sensitivity in the first size classes (Boxmann et al., 1989; Röthele et al., 1989). Besides, the exact parameters for Mie calculation are often not known, especially for aqueous drug solutions. In several studies, it has been shown that the effect of these parameters may be considerable however (Clark, 1995; Müller and Schumann, 1996). It has also been suggested that the absorption coefficient of a droplet is influenced by its diameter and temperature (Boeck 1983). Annapragada and Adjei (1996) concluded for a Malvern 2600 Size Analyzer that Fraunhofer diffraction is accurate for unimodal systems with negligible concentrations outside the declared limits of the lens.

Calculations of the particle size distribution of the aquous tobramycin droplets has been executed with a refractive index of 1.33 and different imaginary values of 0, 0.001, 0.01 and 0.1, assuming that there is zero to very little light absorption. As for other studies, the effect of these parameters on the calculated droplet size distribution appeared to be considerable. Largest differences between Mie and Fraunhofer results for all three nebulizers were found for all three nebulizers for zero imaginary absorption. The differences expressed in percentage of the Fraunhofer value, varied from 58.7 to 28.2% for the X_{10} value, from 16.5 to 11.9% for the X_{50} value and 4.5 to 0% for the X_{90} value. The largest differences in X_{10} value were found for the Freeway Lite, yielding the smallest median droplet size. But the differences were not consistent; they appeared to vary not only with the absolute droplet size, but also with the droplet size distribution. Very remarkable is the observation that with Mie calculation (zero imaginary refractive index), for none of the three nebulizers droplets smaller than 1 μm were calculated, whereas the cascade impactor analysis showed for the PNV that (on average) nearly 12% of the droplets passed the fourth impactor stage, having a cut-off of approximately 1 μm (for droplets with unit density at 40 l/min). Based on these findings

it was decided to use Fraunhofer data only. Furthermore, it should be considered that this study is a comparative evaluation, mainly on the basis of the median diameter (for which differences between both methods are small) and the output rate.

3.2. Comparative nebulizer evaluation

3.2.1. Particle size distribution of the aerosol cloud

In all series of measurements the particle size distribution was evaluated after 10 s, 1.5, 3, 6, 9 and 12 min. The particle size distributions of the selected nebulizers are expressed as X_{10}, X_{50} and X_{90}-values from cumulative percentage undersize curves in Fig. 1. In Table 1 the X_{50} values are presented too. The MMD values are a mean of all measuring times for all three series of measurements.

All nebulizers produced droplets with a X_{50}-value within the wished 1–5 mm range. The relative standard deviation (S.D.) of the individual nebulizers for the X_{50}-value varied from 0.03 to 0.56 mm. For each nebulizer the particle size distribution was not significantly different at the first and the last measurements. Nor were differences observed in between (paired t-test, $P = 0.05$).

In general, the particle size distribution is dependent on the type of nebulizer or the combination of compressor and nebulizer. In the experiments the Sidestream jet nebulizer was combined to three compressors: Porta-Neb, Freeway Lite and DeVilbiss Pulmo-Aide. The Freeway Lite was combined with an older type of the Sidestream. The Porta-Neb and the DeVilbiss were connected to a Sidestream of the same type. The results of these measurements can be compared. The flow rate of the Porta-Neb and the DeVilbiss compressor is 7.0 and 5.3 l/min, respectively. The smaller particle size for the Porta-Neb combination can be explained by the higher flow from the compressor.

When comparing the nebulizers, the results from the particle size distribution experiments

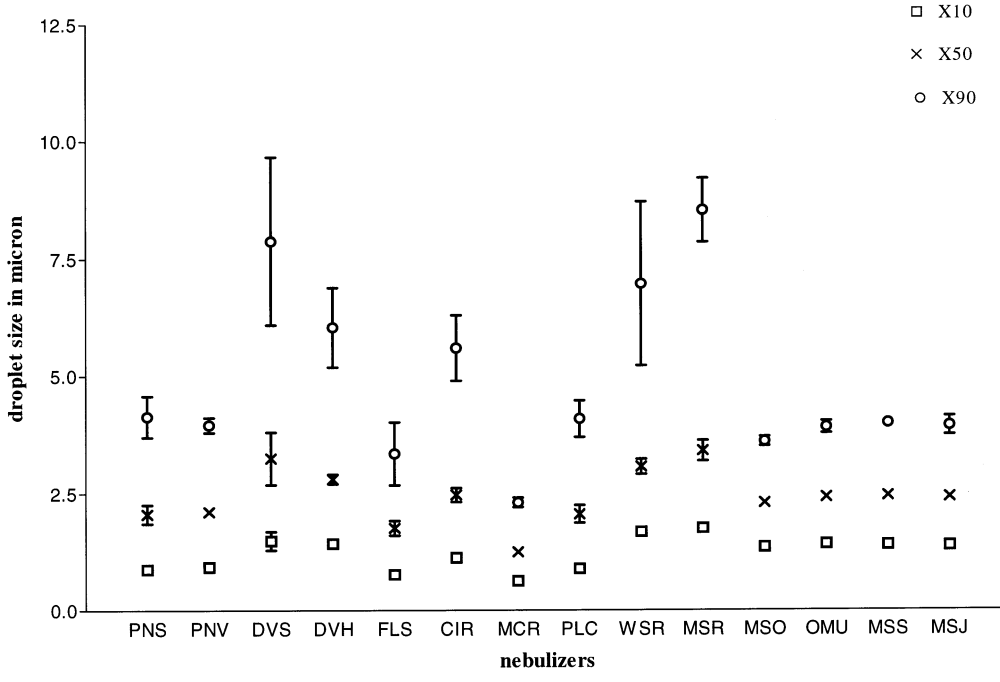

Fig. 1. Represents the droplet size distributions of all nebulizers, expressed as X_{10}, X_{50} and X_{90} values $\pm$ S.D. from cumulative percentage undersize curves. Droplets should be within the range of 1–5 μm.

Table 1
Overview of the results of the nebulization experiments[a]

Nebulizer	J/U	X_{50} (S.D. (μm))	Neb. time (min)	Mean output rate (mg/min) (S.D.)	Concentration after neb. (% m/v) (S.D.)
Porta-Neb Sidestream	j	2.06 (0.20)	6	25.1 (8.5)	12.4 (0.9)
Porta-Neb Ventstream	j	2.11 (0.09)	6	39.3 (4.3)	11.2 (1.3)
DeVilbiss Pulmo-Aide Sidestream	j	3.25 (0.56)	12	9.1 (0.7)	11.1 (0.9)
DeVilbiss Pulmo-Aide Hudson T updraft	j	2.81 (0.10)	12	10.4 (3.2)	10.5 (0.4)
Freeway Lite Sidestream	j	1.76 (0.16)	9	15.7 (3.7)	13.2 (1.4)
Cirrus	j	2.47 (0.15)	12	11.2 (2.0)	13.1 (1.2)
MicroCirrus	j	1.25 (0.06)	12	2.0 (1.3)	11.9 (0.7)
Pariboy Pari LC+	j	2.06 (0.19)	6	33.2 (5.1)	11.5 (0.7)
Wisto Senior	u	3.07 (0.16)	6	25.6 (4.3)	12.5 (0.9)
Medasonic Senior	u	3.41 (0.22)	6	39.5 (2.2)	13.2 (0.7)
Medix Sonix 2000	u	2.30 (0.08)	12	18.0 (1.4)	11.5 (1.2)
Omron Ultrasonic	u	2.42 (0.06)	12	6.8 (1.3)	12.2 (0.5)
Medasonic Systam Senior	u	2.45 (0.03)	12	1.2 (1.8)	12.2 (1.0)
Medasonic Systam Junior	u	2.42 (0.08)	12	14.9 (2.3)	13.8 (1.8)

[a] The diameter X_{50} represent 50 volume percentage from cumulative undersize curves. All data are the mean of triplicate series and all measuring times. J, jet nebulizer and U, ultrasonic nebulizer; Neb. Time, time of nebulization.

showed that all investigated devices may be suitable for inhalation of a 10% tobramycin solution. For each nebulizer the main part of the aerosolized tobramycin was within the respirable size. Two devices (Wisto and Medasonic senior) had to be measured at an interval basis because of the high amount of relatively large droplets and the wide angle of the discharge cone from the mouthpiece. Because of this observation they may be less suitable for clinical use.

3.3. Output rate

The output rates in ml/min of aerosolized tobramycin solution for the nebulizers are presented in Fig. 2. The output rate is the mean calculated after three runs of nebulization. The output rate differs from 0.06 to 0.50 ml/min.

The difference between the PNS and the DVS can be explained by the different flow rate of the compressors. When comparing the Porta-Neb combinations, the Ventstream was more efficient than the Sidestream for the aerosolization of tobramycin.

The tobramycin output rates in mg/min are presented in Table 1 and Fig. 3.

Regression analyses (Fig. 4) showed a correlation between volume and quantity output ($r = 0.9879$).

The mean output rate was measured as volume (ml/min) and as quantity (mg/min). Volume and quantity output rate are related and both measurements are valid for characterization of the output in the set up. The output rate of the quantity is the more practical parameter since it allows an easy calculation of the inhaled dose. The output rates found in this study varied between 1.2 and 39.5 mg/min. Regarding inhalation and exhalation, in actual patient use the output rate will be lower. Assuming an inspiratory:expiratory ratio of 2:3 an output rate of at least 25 mg/min is required to inhale a dose of 300 mg within 30 min. Therefore, it can be concluded that the output rate of several nebulizers is insufficient. Only five nebulizers met the output requirements of at least 25 mg/min: the PNS, the PNV, the PLC, the Wisto senior and the Medasonic senior.

When the results of the particle size and output rate measurements are combined, a preference for the jet nebulizers appears (PNS, PNV, PLC). One of these nebulizers, the PLC, was also used in the

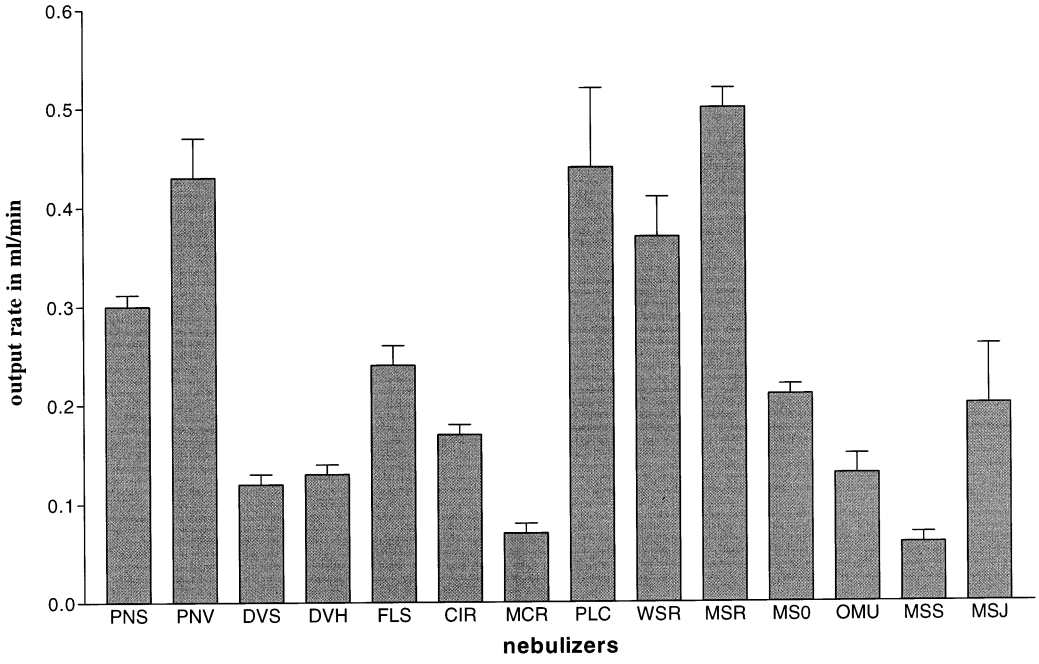

Fig. 2. Represents the mean output rate ± S.D. of tobramycin solution, expressed in ml/min.

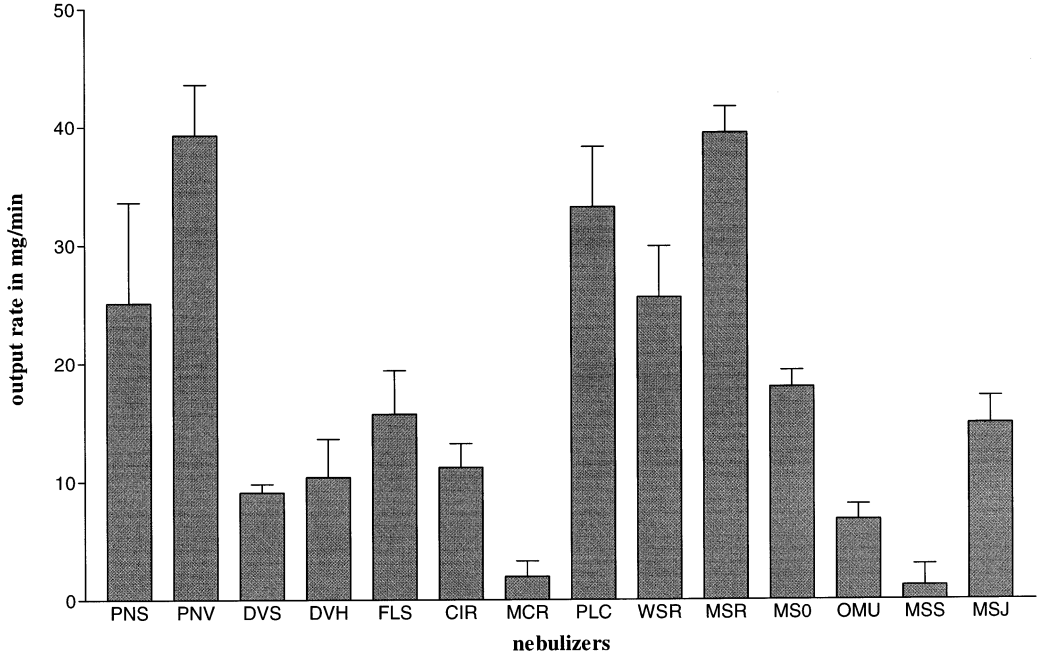

Fig. 3. Represents the mean output rate ± S.D. of tobramycin mass, expressed in mg/min.

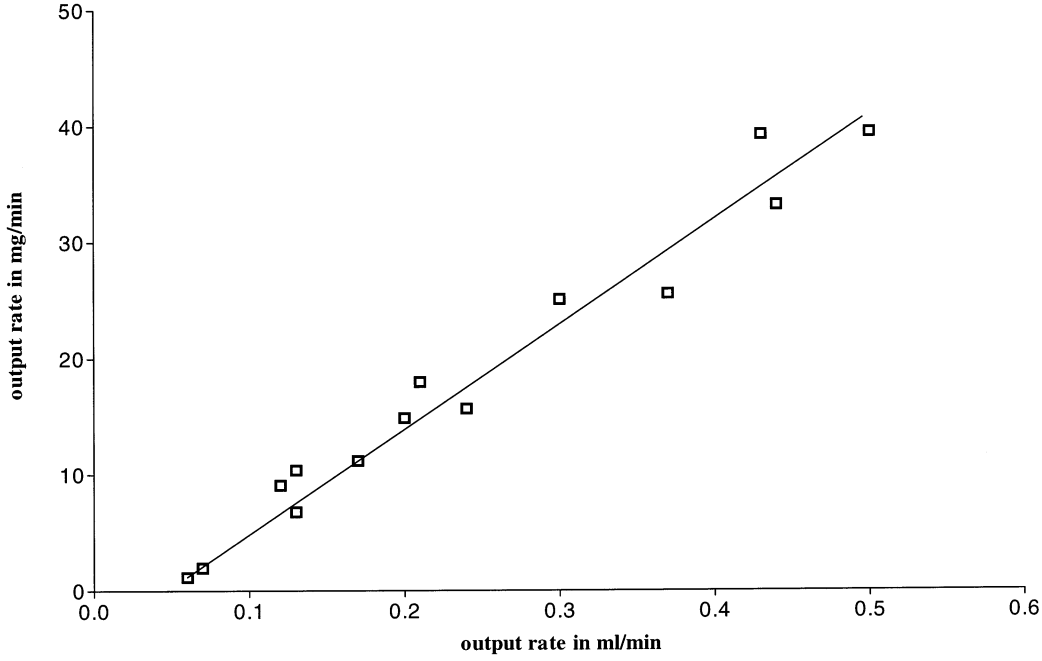

Fig. 4. Represents the correlation between volume and mass output rate ($r = 0.9879$).

study of Ramsey et al. (1999) for the inhalation of 300 mg tobramycin.

When compared to the other jet nebulizers, the higher efficiency of these three nebulizers can be explained by the contribution of the air flow through the open vent. The continuously greater air flow pushes more particles out in a given time, resulting in a higher output rate.

In practical use, the Ventstream and the Pari LC+ will loose less aerosol during exhalation because of the closing of the vent. Therefore, these two nebulizers will have the preference.

3.4. Osmolality, concentration and pH

The osmolality of the 10% tobramycin solution was 230 mOsm/kg. The concentration increased during nebulization due to evaporation of water. After nebulization the concentration ranged from 104.7 to 138.3% of initial. There was no relevant change in pH after the nebulization; both before and after nebulization the pH was 7.5.

As expected, the concentration of the tobramycin solution increased during nebulization due to evaporation of the solvent. This concentration increase, up to almost 40%, had no effect on the droplet size distribution. Since the volumetric output rate and the mass output rate were related, the concentration effect did not result in a less efficient drug output rate.

A 10% solution of tobramycin has an osmolality of approximately 230 mOsm/kg. After nebulization, the maximum value found was 330 mOsm/kg. The osmolality increased from a hypo-osmotic to a somewhat hyper-osmotic value, which will have no clinical implication.

Weber et al. (1997) described that an ideal antibiotic solution should have an osmolality in the range of 150–550 mOsm/kg and, furthermore, should contain a permanent ion in concentrations of 31–300 mM to be readily tolerated in the airway. A 10% tobramycin (as sulphate) has a permanent ion concentration of 177 mM. Regarding osmolality and the permanent ion concentration, a 10% tobramycin solution will be tolerable for inhalation.

4. Conclusions

It was intended to treat patients with a 10% solution of tobramycin without any additives. The choice of a nebulizer is one of the aspects that influence the efficiency of the inhalation treatment.

From this in vitro study, it was concluded that the current formulation of a 10% tobramycin solution is expected to be tolerable and can be administered efficiently with two jet nebulizers: the PNV combination and the PLC combination.

The total amount of tobramycin that can be administered, using a 10% solution, will be 600 mg at most, unless unreasonable inhalation times are accepted. If larger amounts are necessary for adequate treatment, further optimization of the formulation is required.

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