International Journal of Pharmaceutics, 67 (1991) 275–282

 0378-5173/91/$03.50
ADONIS 037851739100105F

IJP 02298

Performance characteristics of the DeVilbiss Ultraneb 99 ultrasonic nebuliser with reference to use in sputum induction

T.R. Leigh [1], T. Nazir [2], J. Wiggins [1], D. Ganderton [2] and J.V. Collins [1]

[1] *Dept of Respiratory Medicine, Westminster Hospital, London SW1P 2AP (U.K.) and* [2] *Chelsea Dept of Pharmacy, King's College, Manresa Rd, London SW3 6LX (U.K.)*

(Received 16 July 1990)
(Accepted 8 September 1990)

Key words: Ultrasonic nebuliser; Sputum induction; Acquired immunodeficiency syndrome; *Pneumocystis carinii* pneumonia

Summary

The DeVilbiss Ultraneb 99 ultrasonic nebuliser is frequently used for sputum induction in AIDS patients undergoing investigation of suspected Pneumocystis carinii pneumonia. We set out to characterise this machine under a wide range of operating conditions so that the efficiency of the technique might be optimised. The range and frequency of particle sizes remained reasonably constant and gave a Gaussian distribution pattern (mean MMD = 5.05 μm, SD = 0.34 μm) below a critical volume of nebulised solution, this volume being related to the intensity setting of the nebuliser. Beyond this volume, the particle size distribution adopted a bimodal pattern, and nebuliser output subsequently tailed off altogether. The volume of couplant within the nebuliser chamber was critical for efficient nebuliser output. Changes in surface tension and tonicity of solution to be nebulised did not affect the performance of the nebuliser substantially. Successful sputum induction may rely on both proximal and distal airway deposition, which may be enhanced by changes in both the nebuliser and nebulised solution.

Introduction

The commonest opportunistic lung infection in the acquired immunodeficiency syndrome (AIDS) is Pneumocystis carinii pneumonia (PCP). This occurs in up to 85% of all patients with AIDS at some time during the course of the disease and carries a mortality of up to 43% (Murray et al., 1984, 1987; Friedman et al., 1989).

Ultrasonic nebulisers are increasingly used in the sputum induction technique (Leigh et al., 1989), which is performed to aid the diagnosis of human immunodeficiency virus (HIV) related opportunistic pulmonary infections. In this technique, which takes between 20 and 30 min to perform, the subject, who cannot produce sputum spontaneously, inhales a mist of nebulised hypertonic saline. The resulting sputum specimen allows identification of *P. carinii* cysts and other pathogens. The mechanisms by which a sputum sample is generated in this technique are not fully understood, but may involve several factors including the induction of local inflammatory and cough responses, a direct osmotic effect on the bronchial mucosa, and variations in the sites of deposition of the nebulised particles (related to particle size). In the lung *P. carinii* are found predominantly in the alveoli (Rankin et al., 1988), and a nebulised

Correspondence: T.R. Leigh, Dept of Respiratory Medicine, Westminster Hospital, London SW1P 2AP, U.K.

particle size of between 1.0 and 2.0 μm is necessary for preferential deposition at this site (Task group on lung dynamics, 1966).

Several groups have suggested that the DeVilbiss Ultraneb 99 ultrasonic nebuliser is the most suitable device available for use in sputum induction (Leigh et al., 1989; Miller et al., 1990). However, its performance characteristics have not been fully documented. This study aimed to evaluate the performance of the nebuliser using a range of different control settings, a variety of nebulised solutions and volumes, to define the best conditions for use of this nebuliser in the sputum induction technique.

Materials and Methods

Nebuliser description

General

The DeVilbiss Ultraneb 99 ultrasonic nebuliser (DeVilbiss, Heston, Middx, U.K.) can operate in one of two ways. In the first of these, the solution to be nebulised is fed continuously into the nebuliser chamber from a reservoir suspended above the apparatus, so that the solution to be nebulised is in direct contact with the nebulising ultrasonic transducer. In the second, the solution to be nebulised is contained in a plastic cup resting on a plastic ring inserted around the top of the nebuliser chamber. The energy from the transducer is transferred through water (which acts as an energy couplant) to the plastic cup containing the solution to be nebulised. The advantage of this second method is that sterilisation of the equipment after use is easily performed by removing the tubing and plastic cup which have been in contact with the patient. However, in the former method, the whole nebuliser chamber would require sterilisation. We thus studied the performance characteristics of the latter mode of operation, which is more suitable for use with potentially infectious patients. The presence of the plastic ring at the top of the nebuliser chamber is important, as without it the plastic cup seats lower in the nebuliser chamber altering the position of the cup relative to the couplant fluid level (see later).

Nebuliser control settings

The nebuliser has two variable controls, a butterfly valve regulating the flow of air over the solution to be nebulised, and an intensity control which changes the amplitude of ultrasonic impulses administered to the solution. The butterfly valve has four marked settings; setting No. 1 reflected 25% valve opening, setting No. 2 was 50% opening, etc. The intensity control is a continuously variable rheostat which has no marked gradations; to define accurately the position of this control for our experiments we placed a scale marked from 0 to 100% around it, coinciding with its maximal anticlockwise and clockwise positions, respectively.

Nebuliser chamber level

In addition to the two manual nebuliser controls, the other performance variable of the DeVilbiss Ultraneb 99 is the volume of water (acting as the energy couplant) placed into the nebuliser chamber. Marks to indicate the manufacturer's suggested maximum and minimum levels are displayed on the outside of the nebuliser chamber.

Measurement of particle size and nebulisation rate

Measurements of particle sizes produced by the nebuliser were made at steady state (after 1 min) by a Malvern 2604c particle sizer (Malvern Instruments, Malvern, U.K.), which uses laser beam diffraction to determine the range of particle sizes passing through it. Two values are quoted, the mass median diameter (MMD) and the *v*.90% which represent the size of particles contained within 50% and 90% by mass of the nebulised mist, respectively. This assumes that the particles are of a constant density. Calculations of nebulisation rate were made by measuring the rate of weight loss from the plastic nebulising cup during a fixed time period, correcting for dead space condensation.

Experiments performed

Effect of varying nebuliser control settings and volume of solution to be nebulised on nebulised particle size and nebuliser output

The first study was to observe the effect on particle size of varying both the nebuliser intensity control setting and volume of solution to be nebulised. Intensity settings ranged from 10 to 100% with solution volumes of between 5 and 80 ml. 3% saline was used with a butterfly valve setting of 4 (maximum). Preliminary studies had shown that the nebuliser was unable to nebulise a solution once a given volume of the solution had been exceeded. This 'critical' cup volume was measured for different intensity settings using 3% saline with a maximum butterfly valve setting.

The effect of changes in the butterfly valve setting on particle size at different intensity settings was measured with 30 ml of 3% saline.

Reproducibility of results was assessed by taking measurements of particle size on five separate occasions with identical nebuliser settings and fluid volumes. These were analysed to establish the coefficient of variation.

Relationship between couplant volume and nebuliser performance

The effects of varying the fluid level in the nebuliser chamber (couplant volume) were determined by measuring changes in both the MMD and the nebuliser output. 30 ml of 3% saline solution were nebulised with a maximum butterfly valve setting, intensity settings varying between 60 and 100% inclusive, and couplant fluid volumes ranging between 120 and 220 ml.

Effect of varying tonicity and character of solution to be nebulised

Tonicity. The effect on MMD of changing the tonicity of the solution to be nebulised was studied

TABLE 1

MMD + (v.90%) values at different intensity settings and solution volumes (nebulised solution, 3% saline; butterfly valve, 4; solid line separates normal from bimodal particle size profiles)

Volume (ml)	Intensity (%)							
	100	80	60	50	40	30	20	10
80	0							
75								
70	1.9 (4.7)							
65								
60	3.7 (9.5)	0						
55				0				
50	4.9 (10.3)	3.8 (9.1)	0	2.5 (39.1)				
45				3.2 (8.4)				
40	5.0 (10.9)	4.8 (10.0)	1.5 (3.2)	3.5 (8.8)				
35								
30	5.2 (11.3)	4.7 (9.9)	4.7 (9.9)	4.8 (9.6)	0			
25				4.8 (9.8)				
20				4.9 (10.0)	4.0 (9.1)	0	0	
15						4.6 (10.0)		0
10					5.3 (10.9)	5.3 (10.9)	5.3 (10.8)	2.0 (6.4)
5	4.7 (9.9)	4.7 (9.9)	5.2 (10.7)	5.0 (10.4)	5.3 (11.0)	5.8 (12.0)	5.6 (11.1)	6.1 (12.2)

using 1, 3, 6 and 10% saline, with variable nebuliser intensity settings; 30 ml of solution were used with a couplant volume of 160 ml and a butterfly valve setting at maximum.

Nebulised pentamidine. Pentamidine isethionate was also studied at its therapeutic concentration of 600 mg in 10 ml water. Both MMD and nebuliser output were measured over a range of intensity settings (40–100%) with a couplant volume of 170 ml.

Surface tension. Surface tension is believed to be an important determinant of nebulised particle size. Thus, the effect of a surface tension lowering agent (Tween 80) on MMD was studied. 30 ml of 1 and 5% saline, with and without 0.5% Tween 80, were studied; surface tension coefficients were measured on a torsion balance. MMD was measured for all four solutions with an intensity setting of 100% and a butterfly valve setting at maximum.

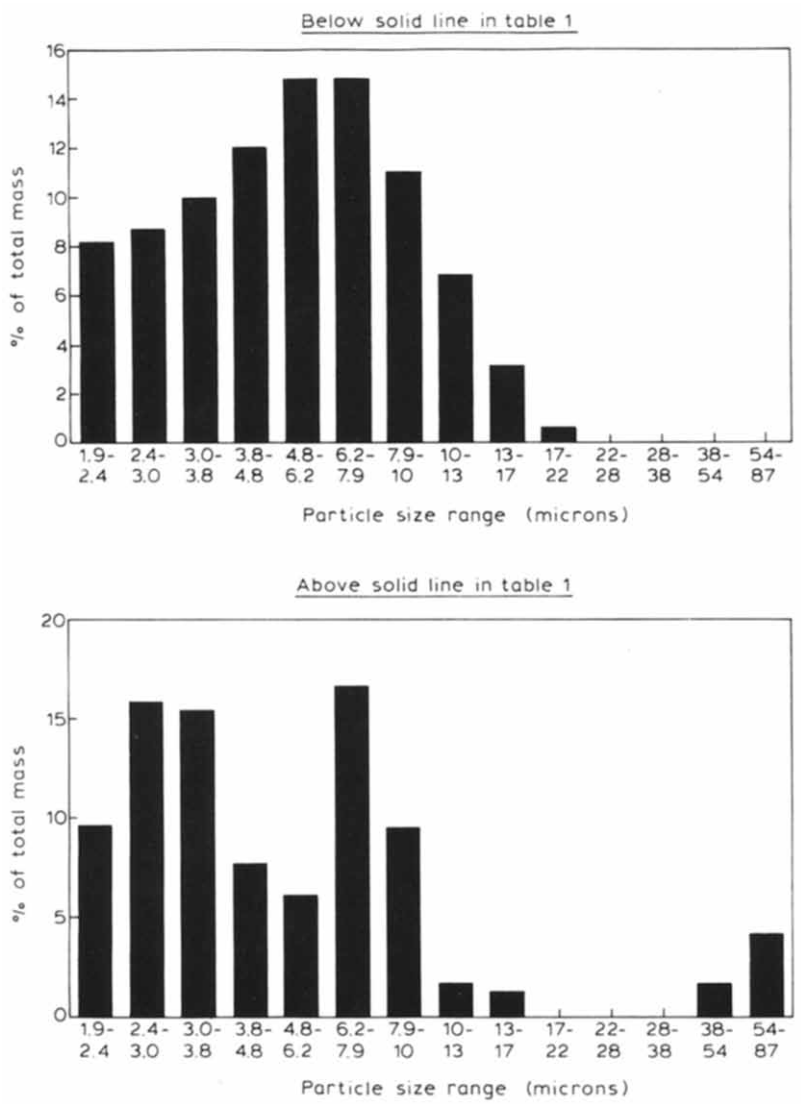

Fig. 1. Graphs showing the two forms of particle size distribution curves, depending on whether nebuliser settings fall above or below the solid line in Table 1.

Statistical analysis. Non-parametric statistical analysis was performed using the Mann-Whitney U test.

Results

Effect of varying nebuliser control settings and volume of solution to be nebulised on nebulised particle size and nebuliser output

The results are shown in Table 1. It was found that within a specified range of nebuliser settings (the area below the solid line in Table 1), the nebulised particle sizes gave a Gaussian distribution (mean MMD = 5.05 μm, SD = 0.34 μm). However, as these settings were progressively altered (above the solid line), the particle size distribution curves initially became bimodal (with an associated fall in MMD, mean MMD = 3.94 μm, SD = 1.32 μm, $p < 0.05$ (see Fig. 1)).

Volume of solution to be nebulised was found to be important for nebuliser output. For a given intensity setting a 'critical' volume was detected above which nebuliser output became negligible (as defined by the inability of the particle sizer to detect nebulised particles). This critical volume was found to increase in proportion to the intensity setting (Fig. 2).

Changing the butterfly valve setting caused only small changes in particle MMD (Table 2), with a maximum variation of 0.5 μm at a given intensity setting.

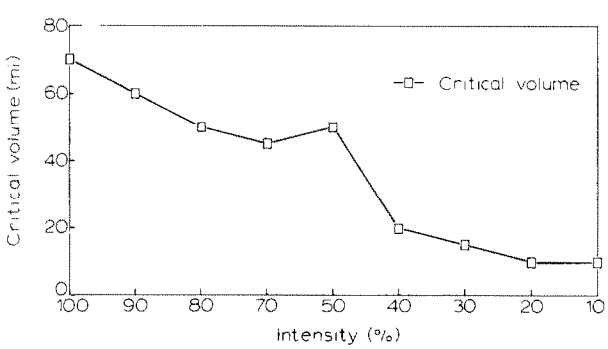

Fig. 2. Graph showing the critical volume of solution to be nebulised for different intensity settings, beyond which there is no detectable nebuliser output.

TABLE 2

MMD (μm) response to changing butterfly settings at different intensities (nebulised solution, 3% saline; cup volume, 30 ml)

Butterfly setting	Intensity (%)		
	100	80	60
1	5.4	5.2	5.1
2	5.6	5.7	5.4
3	5.2	5.2	5.0
4	5.2	5.2	5.0

Measurements of particle size were found to be highly reproducible, with coefficients of variation between 0.6 and 2.4% over the range of intensity settings and solution volumes studied.

Relationship of couplant volume to nebuliser performance

Nebuliser output was found to be significantly affected by both the nebuliser chamber (couplant) fluid volume and the intensity setting (Table 3). In addition, the optimum couplant volume varied with the selected intensity setting from 160 ml at 100% intensity to 180 ml at 60% intensity (Fig. 3). However, the upper and lower limits for the couplant fluid level indicated by the manufacturer corresponded to volumes of 212 and 148 ml, respectively. MMD was minimally affected by

TABLE 3

Nebuliser output and MMD response to changing couplant fluid volume (nebulised solution, 3% saline; butterfly setting, 4)

Couplant volume (ml)	Intensity (%)		
	Flow rate (ml/min) + (MMD μm)		
	100	80	60
220	0.6	0.5	0.5
	(4.0)	(4.5)	(4.6)
200	0.9	0.6	0.4
	(4.2)	(4.3)	(4.3)
180	2.1	1.8	1.1
	(4.8)	(5.2)	(5.2)
160	2.5	1.0	0.3
	(5.4)	(5.3)	(4.9)
140	0.8	0.2	–
	(4.8)	(2.2)	
120	0.1	–	–
	(3.6)		

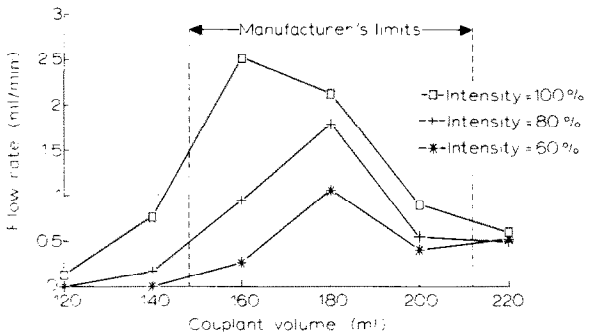

Fig. 3. Graph showing the effect of couplant volume on nebuliser output at different intensity settings. The vertical dotted lines give the suggested limits for couplant volume as recommended by the manufacturer.

changes in couplant volume, mean MMD = 4.5 μm (range 2.2–5.4 μm).

Effect of varying tonicity and character of solution to be nebulised

Tonicity of saline. The effect on MMD of varying the tonicity of nebulised saline solutions was small (Table 4). Over the tested range of 1–10% saline with intensity settings between 60 and 100% the measured MMD varied between 3.7 and 5.7 μm.

Nebulised pentamidine. The MMD of nebulised pentamidine isethionate was not significantly different from that of nebulised saline (Table 5). The MMD varied between 5.3 μm at 100% intensity and 6.1 μm at 40% intensity. The rate of nebulisation rose from 0.7 ml/min (40 mg/min) at 40% intensity to 1.1 ml/min (68 mg/min) at 100% intensity.

Surface tension. Surface tension of both solutions fell following the addition of Tween 80, the torsion value falling from 0.047 to 0.040 N/m with 1% saline and from 0.057 to 0.039 N/m with 5% saline. Small but significant increases in MMD were observed with both 1% (mean MMD 5.1–5.6 μm, $p < 0.01$) and 5% (mean MMD 5.1–5.3 μm, $p < 0.01$) saline solutions following the addition of Tween 80.

TABLE 4

MMD response to different tonicity of nebulised solution at varying intensity settings

Intensity setting (%)	Nebulised solution concentration			
	1%	3%	6%	10%
100	5.6	5.4	5.7	5.1
80	5.5	5.2	5.2	4.9
60	5.2	4.8	4.6	3.7

TABLE 5

MMD values and flow rates of nebulised pentamidine isethionate at different intensity settings

	Intensity (%)			
	100	80	60	40
MMD (μm)	5.3	5.4	5.7	6.1
	5.5	5.5	5.6	5.6
	5.4	5.5	5.6	5.8
Mean	5.39	5.48	5.64	5.84
Flow rate (ml/min)	1.14	0.94	0.79	0.67
mg/min	68.32	56.44	47.53	40.1

Discussion

The purpose of this study was to define the performance characteristics of the DeVilbiss Ultraneb 99 ultrasonic nebuliser under a variety of operating conditions and to relate these characteristics to its use in sputum induction. It was shown that particle MMD of nebulised saline remains almost constant (3.8–6.1 μm) over a wide range of nebuliser operating conditions, which are indicated by the area below the solid line in Table 1. For example, to achieve a constant MMD with an intensity setting of 100% the volume of solution to be nebulised should not exceed 50 ml. However, at an intensity setting of 60% this volume should not exceed 30 ml. Beyond this operational range, MMD values were shown to fall and adopt a bimodal distribution. The reasons for this change in distribution are unclear, but a combination of insufficient energy to nebulise larger particles, and the coalescence of smaller particles to produce a group of larger ones may be involved.

The mechanism by which inhalation of a mist of nebulised saline leads to expectoration of a sputum specimen containing *P. carinii* cysts is unknown. Although the success of sputum induction may be dependent on several factors including stimulation of cough and alveolar deposition of nebulised particles (to 'wash out' *P. carinii* cysts). The sites of distribution of a nebulised mist have been shown to be directly related to its particle size (Task group on lung dynamics, 1966). Theoretically, the ideal mist for sputum induction purposes would contain large particles to induce cough by deposition in proximal airways, and smaller particles for alveolar deposition. Thus, a mist of bimodal particle size distribution with particle size peaks at approx. 2 and 7 μm would be most suitable. Although this distribution pattern was obtained from the DeVilbiss nebuliser under certain operating conditions (above the solid line in Table 1) it was also found that the nebuliser output fell significantly when these conditions were used. This mode of use is impractical for sputum induction as nebulisation of the required volume of solution would take too long. A compromise between obtaining the ideal bimodal size distribution and an adequate nebuliser output would be achieved by delivering a mist with a normally distributed particle size curve at a high flow rate: this is indicated by the solution volumes and intensity settings shown below the solid line in Table 1. The spread of particle sizes is reflected by the v.90% figure, which, if greater than 7 μm, indicates a mist with a significant number of particles in the desired size band. For example, at an intensity setting of 80% with a volume of solution to be nebulised of 30 ml the MMD is 4.7 μm and the v.90% is 9.9 μm. This implies that 40% of the nebulised solution has a particle size between 4.7 and 9.9 μm.

We found that the MMD and (v.90%) obtained from the DeVilbiss Ultraneb 99 ultrasonic nebuliser were significantly greater than those obtained from the Acorn System 22 jet nebuliser (Medic-aid, Pagham, Sussex, U.K.) (unpublished observations), which is used for both sputum induction and the treatment and prophylaxis of PCP. The production of the larger particles by the DeVilbiss Ultraneb 99 suggest that this system is less suitable than the Acorn for the treatment of PCP. Conversely, the latter nebuliser is theoretically less suitable for use in sputum induction, and preliminary observations showing a lower diagnostic sensitivity of the technique when the Acorn nebuliser is used, support this contention.

The effect of correct couplant volume on nebuliser output is clearly shown in Fig. 3. The data show that for optimum nebuliser performance (i.e. a flow rate > 1.5 ml/min) at a given intensity setting, couplant volume should be within a defined range, beyond which the output of the nebuliser falls sharply. This range is narrower than that recommended by the manufacturer. We have also demonstrated that the optimum couplant volume varies with nebuliser intensity setting, and this should therefore be taken into account when setting up the device.

The MMDs of the mist produced when saline solutions of different tonicities were nebulised by the DeVilbiss Ultraneb 99 were similar. Thus, possible differences in the efficacy of sputum induction resulting from the use of saline solutions of varying tonicity are probably due to factors other than the size of the nebulised particles. These may include differences in either stimulation of the cough response, production of a local inflammatory reaction, or effects on mucociliary clearance.

We found that the addition of a surface tension lowering agent (Tween 80) increased the MMD of the nebulised particles generated by the DeVilbiss Ultraneb 99 nebuliser by about 0.5 μm. This increase was unexpected, as a fall in surface tension would normally result in an increase in interfacial surface area with a corresponding reduction in particle size. This suggests that other factors apart from surface tension are involved in determining the nebulised particle size. Although this change in MMD is probably too small to be of practical benefit, larger changes in particle size might be obtainable if greater alterations in surface tension could be achieved.

In conclusion, we have characterised and defined the operating conditions of the DeVilbiss Ultraneb 99 ultrasonic nebuliser. The clinical efficacy of different nebulisers in sputum induction may be the result of both nebuliser output and a

compromise between proximal and distal deposition of nebulised particles, producing cough and alveolar washout, respectively.

References

Friedman, Y., Franklin, C., Rackow, E.C. and Weil, M.H., Improved survival in patients with AIDS, Pneumocystis carinii pneumonia, and severe respiratory failure. *Chest*, 96 (1989) 862–866.

Leigh, T.R., Parsons, P., Hume, C., Husain, O.A.N., Gazzard, B.G. and Collins, J.V., Sputum induction for diagnosis of Pneumocystis carinii pneumonia. *Lancet*, ii (1989) 205–206.

Miller, R.F., Semple, S.J.G. and Kocjan, G. Difficulties with sputum induction for diagnosis of Pneumocystis carinii pneumonia. Letter to *Lancet*, i (1990) 112.

Murray, J.F., Felton, C.P., Garay, S.M., Gottlieb, M.S., Hopewell, P.C., Stover, D.E. and Teirstein, A.S., Pulmonary complications of the acquired immunodeficiency syndrome. Report of a National Heart, Lung, and Blood Institute Workshop. *N. Engl. J. Med.*, 310 (1984) 1682–1688.

Murray, J.F., Garay, S.M., Hopewell, P.C., Mills, J., Snider, G.L. and Stover, D.E., Pulmonary complications of the acquired immunodeficiency syndrome: An update. *Am Rev Resp Dis.*, 135 (1987) 504–509.

Rankin, J.A., Collman, R. and Daniele, R.P. Acquired immune deficiency and the lung. *Chest*, 94 (1988) 155–164.

Task group on lung dynamics, Deposition and retention models for internal dosimetry of the human respiratory tract. *Health Phys.*, 12 (1966) 173–207.