J. Pharm. Pharmacol. 1992, 44: 7-9
Received May 30, 1991

Comparison of Nebuliser Efficiency for Aerosolizing Pentamidine

DON SMITH, DAVID ERSKINE, JANICE STEELE, DENISE HILLS AND BRIAN GAZZARD

Departments of Medicine, Pharmacy and Physiotherapy, St Stephen's Hospital and King's College, University of London, UK

Abstract—Inhaled pentamidine has become an important method of treatment and prophylaxis for *Pneumocystis carinii* pneumonia and we have compared nebuliser efficiency in terms of drug output and droplet sizes in four brands of jet nebuliser (Acorn-22, Inspiron, Cirrus, Respirgard II) and one brand of ultrasonic nebuliser (Fisoneb), at 2 pentamidine concentrations and 3 flow rates, using a laser particle sizer. Droplet size (which varied from 1·2 to 4·7 μm mass median diameter) was dependent in all cases, except with the Respirgard II system, on the flow rate of the gas driving the equipment and the concentration of pentamidine used. Drug output varied significantly between nebuliser brands and for a 300 mg dose of pentamidine was: 61% for the Acorn-22, 62% for the Inspiron, 49% for the Fisoneb and 43% for the Respirgard II. Both droplet size and drug output are important in determining nebuliser efficiency.

Inhaled pentamidine is a licensed treatment and prophylaxis against *Pneumocystis carinii* pneumonia (PCP), both in the UK (Anonymous 1990) and the USA (Centers for Disease Control 1989). *Pneumocystis pneumonia* is an alveolar infection and studies both in animal models of PCP (Girard et al 1987) and in man (Conte & Golden 1988) indicate that high lung levels of drug, with low systemic absorption, can be achieved by inhaling a nebulised solution of pentamidine. Various studies of acute treatment and prophylaxis using nebulised pentamidine have shown this to be an effective regime in HIV antibody-positive individuals, with minimal toxicity (Montgomery et al 1987; Smith et al 1991).

The optimal particle sizes generated by nebulisers to deposit drug in alveoli has been defined for aerosolised antibiotic therapy (Gerrity et al 1979). Most of the previous studies of nebulisers used for inhaled pentamidine therapy have concentrated on particle sizing, which may be influenced by factors such as the concentration of the drug, the flow rate of gas used to drive the instrument and variations in characteristics of individual nebulisers. Less attention has been paid to the amount of drug retained within different nebuliser systems. In this paper these factors have been studied in the laboratory for five commercially available nebuliser systems which are in use in the UK or North America (Lawson et al 1989; Leoung et al 1990).

Materials and Methods

Four brands of jet nebuliser were studied: the Inspiron mini-neb (Bard Ltd, UK), Acorn system 22 (Medic-Aid Ltd, UK), Cirrus (Intersurgical Ltd, UK) and the Respirgard II (Marquest Medical Products, USA). The Acorn system 22 was also tested with a conservation chamber (the Mizer). An ultrasonic nebuliser, the Fisoneb (Fisons Corp., USA) was tested at maximum setting. Four commercially obtained nebulisers of each brand were used.

Correspondence: B. G. Gazzard, Consultant Physician, Westminster Hospital, Horseferry Road, London SW1, UK.

Particle sizing

The droplet size for each of these 20 nebulisers was calculated using a 2600 HSD Laser Particle and Droplet Analyser (Malvern Instruments Ltd). The experiments were carried out at a constant room temperature (22°C) and the nebulisers were placed such that the tip of the mouthpiece was 2·5 cm from the laser beam so that the aerosol passed through it, scattering light. The analyser translated the distribution of scattered light and calculated the fraction of aerosol mass contained within each of 15 size bands using a model-independent computer programme (Newman et al 1985). Nebulisation was performed using a constant flow rate of 6 and 8 L min^{-1} from a compressed gas cylinder or using a Portaneb 50 electric compressor (Medic-Aid Ltd) (this compressor gives flow rates equivalent to 6–8 L min^{-1} according to the manufacturers' specifications and is widely used in the community to administer pentamidine). Each experiment was performed on six separate occasions at each flow rate for the four jet nebulisers. The ultrasonic nebuliser (Fisoneb) was run at maximum setting on six separate occasions. These experiments were performed at two concentrations of pentamidine isethionate (May and Baker Ltd, UK), one that is commonly used in PCP prophylaxis (300 mg pentamidine dissolved in 5 mL Water for Injection (BPC)) and the other for treatment (300 mg in 3 mL of water).

From these experiments the following results were calculated: (1) the mass median diameter (MMD) in μm, i.e. the droplet diameter such that half the aerosol mass is contained in smaller droplets and half in droplets larger than the MMD, (2) the percentage of aerosol mass contained in droplets less than 5·0 μm in diameter as droplets smaller than this are most likely to be deposited in the alveoli (Gerrity et al 1979).

Output studies

The time taken for these instruments to completely nebulise all the drug solution was timed with a stopwatch. Complete nebulisation was defined as a period of 30 s after the last visible release of aerosol.

The total amount of drug nebulised over this period was calculated from measurement of the amount of drug left

within the nebuliser system. This was assessed by thoroughly washing the units at the end of each experiment with 200 mL of distilled water. A portion of the wash solution was then diluted (1:25) and the UV absorbtion was measured at 262·5 nm. A calibration curve was constructed using known concentrations of pentamidine and this allowed the amount of drug retained in the system at the end of nebulisation to be calculated. The amount of drug released was inferred by subtracting the amount left in the nebuliser from the mass of drug originally added to the system. The procedure was repeated twice for each of the nebuliser systems.

From the combined results of the particle sizing and drug output experiments (based on the assumption that pentamidine content was proportional to particle size) it was possible to calculate the mass output of each nebuliser contained within droplets of less than 5 μm (Newman et al 1985).

Statistical analysis

Multivariant analysis (ANOVA analysis [software package: SPSS/PC+Version 2.0, SPSS Inc. Chicago, Illinois]) was performed to assess the differences between nebuliser models at each flow rate and at each concentration.

Results

Particle sizing

The mass median diameter was outside the optimum range for the following nebulisers: the Cirrus, when used at the prophylaxis concentration of pentamidine, the Inspiron when driven by the Portaneb compressor and the Acorn with Mizer spacer when driven at 6 L min^{-1} and with the Portaneb compressor (Table 1). The individual MMDs produced did not fall into a bell shaped normal distribution curve and so it was not valid to calculate the standard deviation for each brand of nebuliser.

Table 1. Mass median diameter (MMD) produced by different nebulisers at different flow rates and drug concentrations.

Nebuliser	Flow rate	Pentamidine (300 mg/5 mL) MMD (μm)	Pentamidine (300 mg/3 mL) MMD (μm)
Inspiron	8 L min^{-1}	3·5 (3·4–3·7)	4·0 (3·8–4·2)
	6 L min^{-1}	4·6 (4·3–4·8)	5·3 (5·0–5·4)
	Portaneb	5·1 (4·6–5·3)	4·3 (4·2–4·4)
Cirrus	8 L min^{-1}	*	3·0 (2·8–3·2)
	6 L min^{-1}	*	4·3 (4·1–4·4)
	Portaneb	3·7 (3·6–3·8)	3·6 (3·4–3·7)
Acorn	8 L min^{-1}	2·5 (2·2–2·7)	3·0 (2·9–3·2)
	6 L min^{-1}	3·1 (3·0–3·2)	4·0 (3·9–4·1)
	Portaneb	3·5 (3·3–3·7)	3·4 (3·2–3·6)
Acorn+Mizer	8 L min^{-1}	3·9 (3·7–4·2)	
	6 L min^{-1}	5·1 (4·9–5·3)	
	Portaneb	5·2 (5·0–5·5)	
Respirgard II	8 L min^{-1}	1·2 (1·2–1·2)	
	6 L min^{-1}	1·2 (1·2–1·2)	
	Portaneb	1·2 (1·1–1·2)	
Fisoneb		4·7 (4·7–4·7)	

* Not measurable due to bubbling. $P<0·001$ for all MMDs. MMD range is given in parentheses.

There were significant differences in the average MMD produced by each of the brands of nebuliser when compared at the same flow rate and the same concentration ($P<0·001$), with the Respirgard II system giving the smallest MMD (Table 1).

The mass median diameter of droplets produced by the Respirgard II system was not dependent on the flow rate, over the range tested, but the other nebulisers performed significantly better ($P<0·001$) at 8 L min^{-1} than at 6 L min^{-1} or with the Portaneb.

The MMD of particles was significantly smaller ($P<0·001$) for the lower concentration of pentamidine (300 mg: 5 mL water) for the 3 brands of nebulisers tested (Cirrus, Inspiron and Acorn) (Table 1).

Output studies

The nebulisation times were considerably longer with the Respirgard II system than with other models (Table 2).

Table 2. Nebulisation time.

		Time (min)	s.d.
Inspiron	8 L min^{-1}	12·05	0·58
	Portaneb	14·7	0·98
Acorn	8 L min^{-1}	12·05	0·8
	6 L min^{-1}	12·6	1·09
	Portaneb	16·7	0·95
Respirgard	8 L min^{-1}	23·2	1·75
	6 L min^{-1}	24·3	1·28
	Portaneb	30·05	1·81
Fisoneb		4·0	0·28

s.d. = standard deviation.

The amount of drug retained within the nebuliser at the end of operation is shown in Table 3. The total amount of drug released was significantly smaller for both the Respirgard II system and the Fisoneb when compared with either the Inspiron or Acorn systems ($P<0·001$).

Table 3. Nebuliser output and efficiency from 300 mg pentamidine dissolved in 5 mL water.

Nebuliser		Mass of drug released as aerosol (mg)±s.d. (%)	Mass of total drug in droplets <5·0 μm (mg) (%)
Inspiron	8 L min^{-1}	186·7±11·35 (62·2)	121·5 (40·5)
	Portaneb	199·7±6·5 (66·6)	98·3 (32·7)
Acorn	8 L min^{-1}	183·2±7·4 (61·1)	136·7 (45·3)
	Portaneb	189·0±13·1 (63·0)	123·2 (41·0)
Respirgard	8 L min^{-1}	130·4±19·1 (43·5)	125·6 (41·9)
	Portaneb	124·8±17·0 (41·6)	117·4 (39·1)
Fisoneb		147·4±0·3 (49·1)	82·7 (27·6)

s.d. = standard deviation.

Discussion

The size of nebulised particles is of crucial importance for the deposition of drug within alveoli. The alveolar deposition of particles probably reach a peak with particles of an MMD of 3 μm. Above 5 μm more particles will be deposited in the

oropharynx and large airways (Newman & Clarke 1983) and may lead to cough (Montgomery et al 1987) and bronchial irritability (Smith et al 1988). Very small particles (< 1 μm) tend not to be deposited in the alveoli as the majority remain contained in the exhaled air (Newman 1985). However, measuring particle sizes alone may give false impressions of nebuliser efficiency, as output varies considerably between nebulisers (43–62% of initial drug). This study also highlights the importance of flow rate and drug concentration on achieving a suitable droplet size for pentamidine solutions. We found that a flow rate of 8 L min^{-1} or a less concentrated solution improved the MMD, the percentage of particles less than 5·0 μm and the amount of drug released as aerosol for all units tested, with the exception of the Respirgard II. Such improvements may increase alveolar penetration of pentamidine by greater than 50% (O'Doherty et al 1990).

The investigations reported here suffer from the disadvantage that no account is taken of variations in nebuliser performance during the respiratory cycle, which may also affect drug deposition in the alveoli (Pavia et al 1977).

It is not clear what effect these differences in nebuliser characteristics have in the clinical context, but other studies indicate that such factors may cause large variations in the amount of pentamidine reaching the alveoli (O'Doherty et al 1990). Reports of treatment (Godfrey-Faussett et al 1988) and prophylaxis failures (Lowery et al 1988) and of upper lobe recurrences (Abd et al 1988) would indicate that adequate peripheral lung levels have not been achieved in some cases. It is likely that nebuliser efficiency (particle size and output) and operating conditions (flow rate and drug concentration) play an important part in these failures. Apart from nebuliser efficiency one of the major reasons for prophylaxis failure in clinical practice is patient compliance (Opravil et al 1990) and thus factors such as length of nebulisation times, patient acceptability and freedom from local side effects are also likely to be of importance.

Acknowledgements

We wish to thank the following people for their help and advice: Professor J. M. Newton and Dr K. Taylor (London School of Pharmacy), Professor D. Ganderton (King's College, Chelsea), Mr M. Sothinanan (Quality Control Department, St Bartholomew's Hospital) and Dr P. Milligan (Head of Statistics and Computing, King's College, London). We also wish to thank May and Baker Ltd for providing pentamidine isethionate and Medic-Aid Ltd, Bards Ltd, Intersurgical Ltd, Fisons Corp. and Marquest Medical Products for providing the nebuliser units tested.

References

Abd, A. G., Nierman, M. D., Ilowits, J. S., Pierson, R. N., Bell, A. L. L. (1988) Bilateral upper lobe *Pneumocystis carinii* pneumonia in a patient receiving inhaled pentamidine prophylaxis. Chest 94: 329–331

Anonymous (1990) Pentamidine isethionate. British National Formulary 20: 226

Centers for Disease Control (1989) Guidelines for the prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with the human immunodeficiency virus. MMWR 38 (Suppl. 5): 1–9

Conte, J. E., Golden, J. A. (1988) Concentrations of aerosolised pentamidine in bronchoalveolar lavage, systemic absorption and excretion. Antimicrob. Agents Chemother. 32: 1490–1493

Gerrity, T.R., Lee, P.S., Hass, F.J., Marinelli, A., Werner, P., Lourenco, R.V. (1979) Calculated deposition of inhaled particles in the airway generations of normal subjects. J. Appl. Physiol. 47: 867–873

Godfrey-Faussett, P., Miller, R.F., Semple, S.J.G. (1988) Nebulised pentamidine Lancet i: 645–646

Girard, P. M., Brun-Pascaud, M., Farinotti, R., Tamisier, L., Kernbaum, S. (1987) Pentamidine aerosol in prophylaxis and treatment of murine *Pneumocystis carinii* pneumonia. Antimicrob. Agents Chemother. 31: 978–981

Lawson, L., Montaner, J. S. G., Falutz, J., Hyland, R., Rachlis, A., Gervais, A., Rennzi, P., McFadden, D., Fong, I.W., Garber, G.E., Martel, A., Schlech, W., Louie, T., Chan, C. (1989) Placebo controlled Canadian co-operative trial of aerosolized pentamidine for the secondary prophylaxis of AIDS-related PCP. Clin. Invest. Med. 12: B93

Leoung, G. S., Feigal, D. W., Montgomery, A. B., Corkery, K., Wardlaw, L., Adams, M., Busch, D., Gordon, S., Jacobson, M. A., Volberding, P. A., Abrams, D., and the San Francisco County Community Consortium (1990) Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia. N. Eng. J. Med. 323: 769–775

Lowery, S., Fallat, R., Geigal, D. W., Montgomery, A. B., Berge, J. (1988) Changing patterns of *Pneumocystis carinii* pneumonia (PCP) on pentamidine aerosol prophylaxis. IV International Conference on AIDS, Stockholm Abstract no. 7167: p. 419

Montgomery, A. B., Debs, R. J., Luce, J. M., Corkery, K. J., Turner, J., Brunette, E. N., Lin, E. T., Hopewell, P. C. (1987) Aerosolised pentamidine as sole therapy for *Pneumocystis carinii* pneumonia in patient with acquired immunodeficiency syndrome. Lancet ii: 480–483

Newman, S. P. (1985) Aerosol deposition considerations in inhalation therapy. Chest 88 (Suppl.): 152–160

Newman, S. P., Clarke, S. W. (1983) Therapeutic aerosols—physical and practical considerations. Thorax 38: 881–886

Newman, S. P., Pellow, P. G. D., Clay, M. M., Clarke, S. W. (1985) Evaluation of jet nebulisers for use with gentamycin solution. Ibid. 40: 671–676

O'Doherty, M., Thomas, S., Page, C., Bradbeer, C., Nunan, T., Bateman, N. (1990) Pulmonary deposition of nebulised pentamidine isethionate: effect of nebuliser type, dose and volume of fill. Thorax 45: 460–464

Opravil, M., Weber, R., Ledergerber, R., Speich, R., Siegenthaler, W., Luthy, R. (1990) Compliance and laboratory data predict relapse rate of *Pneumocystis carinii* pneumonia during prophylaxis with aerosol pentamidine. Klin. Wochenschr. 68: 397–402

Pavia, D., Thompson, M. L., Clarke, S. W., Shannon, H. S. (1977) Effect of lung function and mode of inhalation on penetration of aerosol into the human lung. Thorax 32: 194–197

Smith, D.E., Herd, D., Gazzard, B. G. (1988) Reversible bronchoconstriction with nebulised pentamidine. Lancet ii: 905

Smith, D. E., Hills, D. A., Harman, C., Hawkins, D. A., Gazzard, B. G. (1991) Nebulized pentamidine for the prevention of *Pneumocystis carinii* pneumonia in AIDS patients: experience of 173 patients and a review of the literature. Quart. J. Med. 290: 78: 619–629